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SUSCEPTIBILITY OF MAMMALIAN ERYTHROCYTES TO HEMOLYSIS WITH HYPOTONIC SOLUTIONS

A FUNCTION OF DIFFERENCES BETWEEN DISCOIDAL VOLUME AND VOLUME OF A SPHERE OF EQUAL SURFACE

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Clinicians as well as physiologists have displayed interest in the varied susceptibilities to hemolysis by hypotonic solutions of the erythrocytes of different species of mammals and of human erythrocytes under different pathologic conditions. The variations have been somewhat vaguely ascribed to differences in "osmotic resistance" and in "permeability" due, in turn, to constitutional anomalies and to differences in the age of the erythrocytes. The possibility that differences in the dimensions of erythrocytes might be responsible for differences in susceptibility to hypotonic hemolysis has, however, been mentioned from time to time, and certain correlations in this respect have been pointed out.

Chauffard [1] said he considered that the wide "resistance span" in hemolytic jaundice was an expression of heterogeneity of cell population in respect to diameter. Vallery-Radot and Lhéritier [2] noted that the resistance to hemolysis of the erythrocytes of different species of mammals varied directly with the diameter of the cells. Ponder [3] in

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1. Chauffard, M. A.: Pathogénie de l'ictère congénital de l'adulte, Semaine méd. **27**:25, 1907.

2. Vallery-Rádot, P., and Lhéritier, A.: Parallélisme entre la résistance globulaire aux solutions chlorurées sodiques et la dimension de l'hématie chez les mammifères, Compt. rend. Soc. de biol. **82**:195, 1919.

3. Ponder, E.: The Measurement of Red Cell Volume: VI. The Different "Fragility" of the Red Cells of Various Mammals, J. Physiol. **83**:352 (Feb. 9) 1935.

a recent paper has presented a correlation between the resistance to hemolysis and the volume of the erythrocyte after conversion to a spherical form. None of these observations, however, has more than suggested that the dimensions of the erythrocyte are in some way closely related to the problem, for none has satisfactorily depicted a mechanism at work under the experimental conditions of the "resistance" test.

In 1922 Gänsslen [4] suggested a dynamic explanation of the characteristically increased susceptibility of the erythrocytes of chronic familial hemolytic jaundice to destruction by hypotonic solution of sodium chloride. His statement may be translated as follows:

> The fact that in the microcytes of hemolytic jaundice one is dealing with altered, namely, approximately spherical, erythrocytes, averaging larger than normal in volume, allows one to explain the decreased resistance in the following manner: The active forces in resistance experiments are osmotic forces. The sphere is the form which has the greatest volume with the least surface; it contains the greatest amount of paraplasm in the smallest envelop. Therefore, in order to reach osmotic equilibrium, the erythrocytes of hemolytic jaundice will take up more water than normal erythrocytes. Because of their form, however, they will be less capable of accommodating it. Their effort to take up more water results in a disproportion to the size of the envelop, which in resistance experiments finds its expression in an early destruction or rupture of the cell, so that hemolysis begins in much higher concentration than normal.

Gänsslen presented no experimental data supporting his hypothesis except a few measurements confirming the increased cell volume relative to the diameter in hemolytic jaundice, which had already been observed by Naegeli and Alder.[5] Von Boros [6] referred to Gänsslen's work but stated that similarly shaped erythrocytes without altered resistance to hemolysis are found in the blood of patients with anemia due to hemorrhage. Both he and Meulengracht [7] regarded the spherocytosis and decreased resistance in hemolytic jaundice as unrelated phenomena resulting from rapid production of blood. Chauffard [1] and Naegeli [8] considered the decreased diameter and resistance as unrelated and due to a fundamental constitutional defect in the formation of erythrocytes.

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4. Gänsslen, M.: Ueber hämolytischen Ikterus, Deutsches Arch. f. klin. Med. **140**:210, 1922.

5. Alder, cited by Naegeli.[8]

6. von Boros, J.: Ueber Grösse, Volumen und Form der menschlichen Erythrozyten und deren Zusammenhang: II. Die Mikrozytose beim hämolytischen Ikterus, Wien. Arch. f. inn. Med. **12**:255, 1926.

7. Meulengracht, E.: Der chronische hereditäre hämolytische Ikterus, Leipzig, Werner Klinkhardt, 1922.

8. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, ed. 3, Berlin, Walter de Gruyter & Co., 1919, p. 408.

Fortunately, Haden's[9] recent work has again emphasized the differences in the form (thickness-diameter ratio) of erythrocytes of different susceptibility to hemolysis by hypotonic solution. His conclusions are in accord with Gänsslen's hypothesis, which has been extended to an explanation of the differences in susceptibility to hemolysis of the erythrocytes of certain other blood dyscrasias, notably hypochromic anemia. Jacobs[10] has pointed out that considerable differences exist in the increase in volume necessary to produce hemolysis of various types of erythrocytes. He has assumed that because of its biconcave shape the erythrocyte may swell considerably in hypotonic solutions without a significant increase in its original surface. If this is so, it is possible that differences in shape may be entirely responsible for differences in susceptibility to hemolysis and in apparent permeability.

Nevertheless, if differences in the shape of erythrocytes are to explain entirely differences in susceptibility to hemolysis by hypotonic solutions, significant differences in strictly osmotic behavior must be shown not to exist. That is to say, the percentage increase in the original volume of erythrocytes of different susceptibilities to hemolysis must be the same when equilibrium is established with a given hypotonic solution. Moreover, for the support of Gänsslen's hypothesis it is essential to show that differences in shape can quantitatively explain differences in susceptibility to hemolysis. And, finally, further support would be given to the geometric hypothesis if differences in shape, rather than in permeability, could be shown to account for differences in the time necessary for a given hypotonic solution to produce hemolysis of different types of erythrocytes.

EXPERIMENTS

Percentage of Increase in Erythrocyte Volume in Hypotonic Plasma.—Our approach to the problem was to examine the osmotic behavior of erythrocytes of different susceptibilities to hypotonic hemolysis.[11] Determinations were made of the percentage increase in volume of samples of erythrocytes after suspension in progressive dilutions of homologous oxalated plasma. In all, forty-five observations were made on the erythrocytes of normal human beings, dogs, rabbits, pigs and sheep and on the erythrocytes of patients with severe hypochromic anemia and of patients with chronic familial hemolytic jaundice. In each instance a suitable amount of venous blood was rendered incoagulable by the addition of 0.05 cc. of a 20 per cent solution of potassium oxalate to each 5 cc. of blood. The volume of

9. Haden, R. L.: (*a*) The Mechanism of the Increased Fragility of the Erythrocytes in Congenital Hemolytic Jaundice, Am. J. M. Sc. **188**:441, 1934; (*b*) Tr. A. Am. Physicians **49**:308, 1934.

10. Jacobs, M. H.: The Permeability of the Erythrocyte, Ergebn. d. Biol. **7**:1, 1931.

11. Castle, W. B., in discussion on Haden,[9b] p. 326.

the erythrocytes of each sample was then determined by means of the Wintrobe[12] hematocrit tubes. On the basis of this value, homologous oxalated plasma was added to an uncentrifugated portion of the original blood in amounts sufficient to yield a sample with a cell volume of 30 per cent. In a series of nine test tubes 1 cc. of the 30 per cent suspension of erythrocytes was added to such amounts of homologous plasma and distilled water that the original volumes of erythrocytes were suspended in equal amounts of concentrations of homologous plasma of 1, 0.95, 0.9, 0.85, 0.8, 0.75, 0.7, 0.65 and 0.6, respectively. A sample of the erythrocyte suspension in each tube was pipetted into each of two Wintrobe hematocrit tubes. All the hematocrit tubes from one experiment were then placed in the centrifuge at the same time and rotated at 2,500 revolutions per minute for thirty minutes.

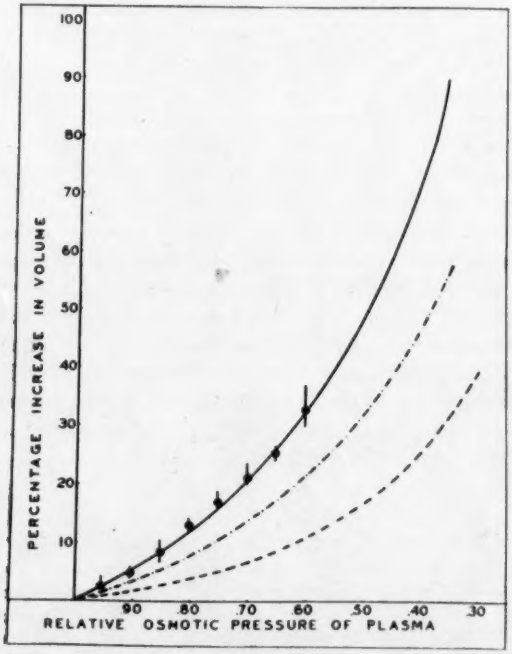

Chart 1.—Average values obtained from forty-five experiments on the percentage increase in equilibrium volume of seven types of erythrocytes in hypotonic oxalated plasma (solid circles). The vertical line through the solid circle shows the extremes of average values obtained for any type of erythrocyte (table 2). The upper curve (solid line) gives the best approximation of the average values and is based on the formula $V_s = [\frac{1\ (100-b)}{P_e} + b] - 100$, the value 51 being used for b. The middle curve is constructed from this formula, the value 69.4 being used for b. The lowest curve is described by a value of 82.9 for b. An explanation of the theoretical significance of these curves is given in the text.

12. Wintrobe, M. M.: The Direct Calculation of the Volume and Hemoglobin Content of the Erythrocyte, Am. J. Clin. Path. **1**:147, 1931.

After centrifugation the volume of erythrocytes was measured in all the hematocrit tubes showing no trace of hemolysis. In table 1 are presented illustrative data obtained from an experiment on the erythrocytes of a dog.

From the averages of the uncorrected duplicate hematocrit determinations were computed the respective percentage increases in the equilibrium volume of the erythrocytes in each plasma concentration over the volume in undiluted plasma in the first tube. In table 2 are shown the average results of all the observations for each species and pathologic condition. The final averages of these values are also shown in table 2 and are plotted as solid circles in chart 1. The vertical lines in chart 1 indicate the extremes of the average data for any type of erythrocyte. The data in table 2 apparently indicate that the observed differences in the per-

TABLE 1.—*Data from Experiment (9/18/35) on Equilibrium Volumes of Dog Erythrocytes*

Concentration or relative osmotic pressure of plasma	1.00	0.95	0.90	0.85	0.80	0.75	0.70	0.65	0.60
Volume percentage of erythrocytes	13.33	13.13	14.01	14.65	14.98	15.67	16.10	16.66	17.29
Duplicates	13.29	13.57	14.02	14.01	15.08	15.50	15.92	17.58	17.35
Average percentage	13.31	13.35	14.01	14.33	15.03	15.63	16.01	17.12	17.32
Absolute increase in equilibrium volume	0.00	0.04	0.70	1.02	1.72	2.32	2.70	3.81	4.01
Percentage increase in equilibrium volume	0.00	0.30	5.30	7.70	12.90	17.40	20.30	28.60	30.10

TABLE 2.—*Average Percentage Increase in Equilibrium Volumes of Various Types of Erythrocytes*

Type of Erythrocyte	No. of Experiments	Concentration or Relative Osmotic Pressure of Plasma*								
		1	0.95	0.9	0.85	0.8	0.75	0.7	0.65	0.6
Hypochromic anemia	8	0	...	5.8	...	14.3	....	22.8	....	37.1
Normal human being	8	0	...	4.7	...	12.9	....	21.5	....	33.2
Dog	5	0	1.8	4.0	6.6	12.2	15.9	20.4	26.5	30.6
Hemolytic jaundice	5	0	2.6	4.6	10.7	12.9	15.9	20.1	24.3	29.8
Rabbit	5	0	2.9	4.2	9.9	13.6	17.4	23.9	H	H
Pig	8	0	0.8	4.9	7.7	12.1	18.9	....	H	H
Sheep	6	0	4.1	5.2	7.8	12.9	16.9	22.3	H	H
Averages		0	2.4	4.8	8.5	12.9	17.0	21.8	25.4	32.6

* H indicates that some hemolysis was present in these concentrations after centrifugation.

centage increase in volume for all the various types of erythrocytes were within the experimental error of the method. Thus the osmotic behavior of the various types of erythrocytes appears to be uniform.

Microscopic Observations of Alteration in Form of Erythrocytes in Hypotonic Plasma.—The problem was, therefore, to account for the wide differences in susceptibility to hypotonic hemolysis of erythrocytes undergoing apparently similar percentage increases in volume in hypotonic plasma. Gänsslen's [4] hypothesis implies that because of the biconcave or invaginated form of the erythrocyte in isotonic solution, swelling is possible without an increase in surface until a spherical form is reached. Attainment of the spherical form will therefore result in destruction of the cell, since thereafter an increase in surface must accompany any further increase in volume. However, it is essential for this hypothesis to assume that the erythrocyte in swelling behaves like a balloon with a liquid interior rather than like a sponge which swells

without changing its form. On this point agreement is not complete, although the critical observations of Ponder and Millar [13] demonstrated a decrease in the diameter of the cell as swelling occurred, and Haden [9] has recently found an increase in the thickness-diameter ratio of erythrocytes in dried films of blood prepared from progressive dilutions of heparinized blood with distilled water. Nevertheless, it seemed desirable to observe under the microscope the changes in form of erythrocytes of different susceptibilities to hypotonic hemolysis when suspended in various dilutions of oxalated plasma, especially when two types of erythrocytes were suspended together in the same hypotonic plasma.

A drop of a dilute suspension of any type of erythrocyte in homologous oxalated plasma was placed on a flat slide and covered with a thin cover glass. Immediately after being sealed with paraffin the preparation was examined under an oil immersion lens with the stage of the microscope in a *vertical* position and illuminated by a strong source of artificial light. In this way a view of different aspects of the corpuscles is obtained as they rotate or oscillate in sinking through the plasma. All types of corpuscles showed the biconcave discoidal or, rarely, the "cup" form in isotonic oxalated plasma. If, however, a suspension of any type of corpuscle was examined in hypotonic oxalated plasma of such concentration that over half the cells were hemolyzed, many of the remaining intact cells were seen to be almost spherical, but some were still somewhat biconcave. If serial observations were made in increasingly dilute samples of plasma, the proportion of almost or entirely spherical cells increased.

That a given concentration of hypotonic plasma had a greater effect on the original form (not volume) of erythrocytes of relatively diminished resistance to osmotic hemolysis than on the form of erythrocytes possessing a greater resistance to hemolysis was best demonstrated by study of a preparation containing two such different types of erythrocytes, for example, a mixture of sheep and human cells. When suspended in suitable human plasma of 0.5 concentration, many of the sheep cells were hemolyzed, but those remaining intact were readily identifiable because of their small size when compared with the human corpuscles. Many of the sheep corpuscles were noted to be almost spherical, sometimes exhibiting only a slight depression or "pip" at one point, whereas the human erythrocytes exhibited a decidedly biconcave form. If, however, human corpuscles were observed in plasma of 0.34 concentration, many of them, like those of the sheep when suspended in plasma of 0.5 concentration, were noted to have become almost spherical.

These observations make it clear that the approach to the spherical form is associated with destruction of each type of corpuscle. Moreover, a concentration of hypotonic plasma producing a large proportion of nearly spherical forms of a given type of erythrocyte produces fewer nearly spherical forms of any type of corpuscle with greater resistance to hypotonic hemolysis.

Calculation of Susceptibility to Hypotonic Hemolysis on the Basis of the Form of the Erythrocyte.—The qualitative behavior of the erythrocytes just described suggests that the swelling of erythrocytes, as implied by Gänsslen's [4] hypothesis and by Jacobs,[10] is not accompanied with an increase in surface until a spherical form is attained. If this is so, the resistance to hemolysis of a given type of erythrocyte might be expressed *by the percentage of difference between the original discoidal volume of the erythrocyte in isotonic solution and the volume of a sphere*

13. Ponder, E., and Millar, W. G.: Alterations in the Form of Mammalian Erythrocytes in Hypotonic Plasma, Quart. J. Exper. Physiol. **15**:1, 1925. Millar, W. G.: The Diffraction Method of Measuring the Diameter of Erythrocytes, Proc. Roy. Soc., London, s.B **99**:264, 1926.

with a surface equal to that of the erythrocyte in isotonic solution.[14a] In subjecting this supposition to quantitative test, difficulty is at once encountered because of the impossibility of making accurate measurements of the erythrocyte under the experimental conditions. This obstacle has been fully discussed by Ponder.[14b] Nevertheless, it seemed worth while to attempt to estimate the geometric characteristics of the various samples of erythrocytes which had been studied with regard to equilibrium volumes.

From those observations the uncorrected volume percentage of erythrocytes in each sample of oxalated venous blood was already known. A count of the number of erythrocytes per cubic millimeter in each sample was made, and by means of the formula $\frac{\text{cell volume percentage}}{\text{millions of cells per cubic millimeter}} \times 10 =$ mean corpuscular volume (cubic microns), the uncorrected mean corpuscular volume (V_o) was calculated. Films from each sample of oxalated venous blood were immediately prepared and stained with Wright's stain. From these preparations the mean cell diameter (D_o) was determined by measuring 500 erythrocytes by the method of Price-Jones.[15] The mean corpuscular thickness (T_o) was then calculated by means of the formula $T_o = \frac{4V_o}{\pi D_o^2}$, on the assumption of von Boros[16] that the erythrocyte is a right cylinder of known volume and diameter. The volume, diameter and thickness of this cylinder being known, its surface was found, and finally the volume (V_s) of a sphere with this surface. The percentage of increase in volume necessary to cause the discoidal erythrocyte to assume a spherical form without change in surface would then be represented by the formula $\frac{V_s - V_o}{V_o}$. The essential average data for each type of erythrocyte are shown in table 3.

The observations on the percentage increase in equilibrium volumes of the erythrocytes were made in diluted homologous oxalated plasma in order to avoid the preliminary washing and centrifugating which would have been involved if hypotonic solution of sodium chloride had been employed. Since it was impracticable to obtain sufficient oxalated plasma for determining the range of susceptibility to hemolysis of the erythrocytes of each sample, this information was secured by using appropriate dilutions of solution of sodium chloride according to the method of Worthley and one of us (G. A. D.).[17] A mean value was taken as lying halfway between the concentrations for "definite" and "partial." In quantitative studies of hemolysis this value was shown to correspond fairly well to the steepest part of the S-shaped summation curve obtained, or to about 50 per cent hemolysis. Other observations showed that the range of susceptibility to hemolysis of normal human and sheep erythrocytes in serial dilutions of oxalated plasma cor-

14. Since this manuscript was submitted for publication similar conclusions have been published by Ponder as follows: Ponder, E.: (*a*) The Spherical Form of the Mammalian Erythrocyte: III. Changes in Surface Area in Disks and Spheres, J. Exper. Biol. **14**:267, 1937; (*b*) The Mammalian Red Cell and the Properties of Haemolytic Systems, in Chambers, R.: Protoplasma-Monographien, Berlin, Gebrüder Borntraeger, 1934, vol. 6.

15. Price-Jones, C.: Red Blood Cell Diameters, London, Oxford University Press, 1933.

16. von Boros, J.: Die Behandlung der Anämien, Ergebn. d. inn. Med. u. Kinderh. **42**:635, 1932.

17. Daland, G. A., and Worthley, K.: The Resistance of Red Blood Cells to Hemolysis in Hypotonic Solutions of Sodium Chloride, J. Lab. & Clin. Med. **20**: 1122, 1935.

TABLE 3.—*Average Values for Venous Blood, Average Dimensions and Average Relative Osmotic Pressure for Mean Hypotonic Hemolysis of Various Types of Erythrocytes*

		Venous Blood				Dimensions of Erythrocytes†							
Type of Erythrocyte	Number of Experiments	Erythrocytes, Millions per Cu. Mm.	Hemoglobin, Gm. per 100 Cc.*	Erythrocytes, Volume %	Mean Corpuscular Hemoglobin Concentration %	V_o Microns³	D_o Microns	T_o Microns	S_o Microns²	V_s Microns³	$\frac{V_s-V_o}{V_o}$	V_h	P_h
Hypochromic anemia	8	3.36	6.2	21.1	25.5	63.7	7.03	1.63	114.0	114.6	80.3	86.0	0.363
Normal human being	5	4.85	14.5	41.1	32.4	85.7	7.18	2.11	128.3	136.6	59.5	75.0	0.395
Dog	5	6.76	15.9	48.1	33.0	66.1	6.45	2.01	106.3	103.1	57.1	62.3	0.440
Hemolytic jaundice	6	3.42	11.4	29.1	36.1	84.4	6.88	2.28	122.9	128.0	51.7	48.0	0.505
Rabbit	5	3.97	9.4	30.7	30.7	70.9	6.22	2.34	106.7	103.4	46.1	43.4	0.530
Pig	4	8.23	14.6	45.3	32.3	51.9	5.47	2.21	85.3	74.2	42.9	38.5	0.560
Sheep	4	9.39	11.3	35.5	33.0	35.4	4.14	2.63	61.4	45.1	27.4	30.0	0.620

* 15.6 Gm. equals 100 per cent.

† V_o indicates mean corpuscular volume; D_o, mean corpuscular diameter; T_o, mean corpuscular thickness $\left(\frac{4\ V_o}{\pi\ D_o^2}\right)$; S_o, mean corpuscular surface $\left(\pi\ D_oT_o + \frac{\pi\ D_o^2}{2}\right)$; V_s, volume of sphere with surface, S_o; $\frac{V_s-V_o}{V_o}$, percentage increase in volume of spherical form (V_s) over discoidal form (V_o); V_h, $\left[\frac{1(100-51)}{P_h}+51\right]-100$, percentage increase in volume of discoidal form at relative osmotic pressure for mean hemolysis; P_h, relative osmotic pressure for mean hemolysis.

responded sufficiently closely to that in hypotonic solution of sodium chloride, so that a 1 per cent solution of sodium chloride could be considered approximately isotonic with undiluted oxalated plasma.

In chart 2 are plotted the results of calculations of the value $\frac{V_s - V_o}{V_o}$ based on data obtained from individual observations on the erythrocytes of thirty-seven samples of blood. Each value is plotted as the ordinate against the relative osmotic pressure observed to produce 50 per cent hemolysis of the particular sample of erythrocytes as the abscissa. Inspection of the points shown in chart 2 suggests that they fall in general along the extrapolation of the observed curve of percen-

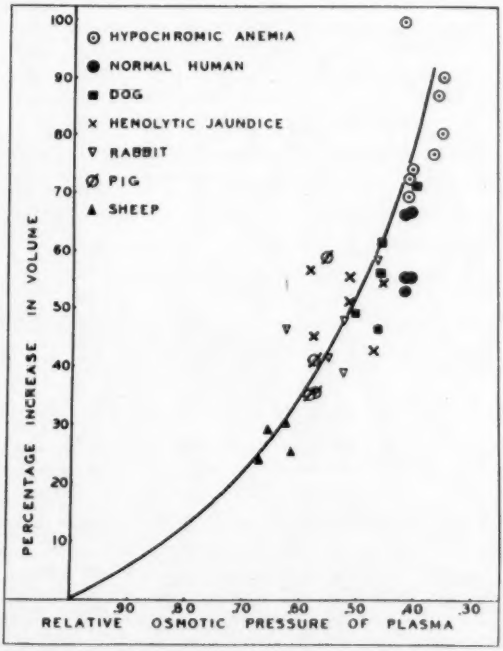

Chart 2.—The percentage increase in discoidal volumes of samples of individual erythrocytes, calculated from formula $\frac{V_s - V_o}{V_o}$, compared with the percentage increase in discoidal volumes at relative osmotic pressures for mean hemolysis, derived by extrapolation of the average curve for equilibrium volumes shown in chart 1.

tage increase in volume, which is identical with that shown as a solid line in chart 1. In table 3 are presented the average values of $\frac{V_s - V_o}{V_o}$ for each of the various types of erythrocytes, arranged in the order of increasing susceptibility to hypotonic hemolysis. This order was paralleled by the values of $\frac{V_s - V_o}{V_o}$ and, except for the normal human erythrocyte, the numerical correspondence with the percentage increase in equilibrium volume (V_h) at the relative osmotic pressure for mean hypotonic hemolysis (P_h) was reasonably good.

Correlation of Apparent Differences in Time of Hemolysis of Erythrocytes with Differences in Discoidal Form.—In dealing with the rate of entry of water into spherical cells in hypotonic solution, measurement of the increase in volume at any moment can be made by determination of the diameter. Because this method is obviously not applicable to nonspherical cells, such as erythrocytes, since the work of Hamburger, the appearance of hemolysis has been applied to determinations of the permeability of erythrocytes. Jacobs [10] has pointed out the various limitations of this method, including the difficulty of using hemolysis as the indicator of increase in volume for nonspherical cells which may undergo considerable or different increases in volume before the surface begins to be extended. He has presented a formula for expressing the rate of entry of water based on the assumption that the surface of the erythrocyte does not increase during the swelling process. Since this is precisely the assumption involved in Gänsslen's explanation of differences in susceptibility to hemolysis when osmotic equilibrium is established, further evidence of its validity might be obtained by study of the time required for hemolysis of different types of erythrocytes. On the assumption that differences in this time are due not to differences in permeability but to differences in the value $\frac{V_s - V_o}{V_o}$, a relationship to the increase in volume possible without change in surface might be apparent.

TABLE 4.—*Time Required for 75 Per Cent Hemolysis of Various Types of Erythrocytes in a 0.02 Molar Solution of Sodium Chloride*

Species	Observed Time, Seconds*	Calculated Time, Seconds	
		$k = 0.3758 \times 10^{-4}$	$k = 0.39 \times 10^{-4}$
Man	8.35	**8.35**	6.56
Dog	6.10	5.15	4.76
Rabbit	3.00	3.53	3.40
Pig	3.00	2.75	2.68
Sheep	1.90	1.91	**1.90**

* After Jacobs.[10] The figures in boldface type are the basis for the calculations of the respective values of k.

Jacobs [10] has presented data on the time required for 75 per cent hemolysis of erythrocytes of several types of animals after the sudden mixing of a small amount of defibrinated blood with a large volume of two-hundredths-molar solution of sodium chloride. His studies included erythrocytes for which we have pertinent data, namely, those of man, dog, rabbit, pig and sheep. The respective times observed by Jacobs for 75 per cent hemolysis of the erythrocytes of these species at 20 C. are given in table 4.

From these data, according to Jacobs' formula for the rate of entry of water, the permeability constants of the human and the sheep cell, respectively, were calculated as follows:

$$k = \frac{p_o V_o}{P^2 A t} \ln \frac{p_o V_o - P V_o}{p_o V_o - P V_s} - \frac{V_s - V_o}{P A t}$$

utilizing our values for the cell dimensions. In Jacobs' formula k is the permeability constant; t, the time in seconds required for 75 per cent hemolysis; A, the constant surface of the erythrocyte; V_o and p_o are the initial volume and osmotic pressure, respectively, of the erythrocyte in defibrinated blood (considered isotonic with 1 per cent solution of sodium chloride); V_s and P are, respectively, the spherical volume and the constant external osmotic pressure (two-hundredths-molar sodium chloride). Determination of the value of k for the human cell gave 0.3758

$\times 10^{-4}$, and for the sheep cell 0.39×10^{-4}. Using each value, the times required theoretically for hemolysis of the other types of erythrocytes were then determined by means of Jacobs' formula and are shown in table 4 for comparison with the actual times observed by Jacobs.

Inspection of the data given in table 4 suggests that the theoretical values are at least of the order of magnitude to be expected on the basis of the assumption that differences in shape may account for differences in the time required for hemolysis. Jacobs' observations, as well as our own, are merely averages for each type of erythrocyte. Better correspondence might have resulted had the experiments been made by one observer on the same samples of each type of blood. It is not suggested that differences in the rate of penetration of water do not exist but that in the absence of more direct evidence the apparent differences in the times of hemolysis of different types of erythrocytes may be explained by differences in the forms of the erythrocytes.

COMMENT

The data in table 2 suggest that the percentage increases in volume of erythrocytes of different susceptibilities to hypotonic hemolysis are not significantly different. Nevertheless, the question arises whether, despite appearances to the contrary, sufficient differences exist to account entirely for the differences in susceptibility to hemolysis. In order to settle this question, theoretical percentage increases in volume of the various types of erythrocytes were calculated on the assumption that the greater the susceptibility to hemolysis of any type of erythrocyte, the greater would be the percentage increase in its equilibrium volume.

To effect this, it was first necessary to have a mathematical expression describing the average observed percentage increases in volume shown in table 2. For this purpose it is immaterial whether the effects observed are associated with an osmotically inactive cell component [18] or with "leakage" of osmotically active substance out of the erythrocyte.[19] The equation used by Lucké and McCutcheon,[18] $V_e = \frac{P_o(V_o - b)}{P_e} + b$, expresses the law of Boyle-van't Hoff as applied to cells containing a nonosmotically active fraction. As applied to our experiments, P_o and V_o stand, respectively, for the relative osmotic pressure of the undiluted oxalated plasma and the volume occupied by the erythrocytes in this plasma. The constant, b, represents the osmotically inactive volume of the erythrocyte. The theoretical values for V_e and P_e giving the best approximation to the average observed values (table 2) were obtained by using a value for b of 51 per cent of V_o. With this value, the curve shown in chart 1 was plotted and extrapolated beyond the range of the observed values according to the formula $V_e = \left[\frac{1\ (100-51)}{P_e} + 51\right] - 100$. Since the result desired is the

18. Lucké, B., and McCutcheon, M.: The Living Cell as an Osmotic System and Its Permeability to Water, Physiol. Rev. **12**:68, 1932

19. Ponder, E.: The Kinetics of Hemolysis, Physiol. Rev. **16**:19, 1936.

percentage increase in volume, the original volume occupied by the erythrocytes (V_o) was taken as 100, and the relative osmotic pressure of the undiluted plasma (P_o) was taken as 1.

By the methods previously described, approximately 50 per cent of the sheep corpuscles were found to be hemolyzed in a concentration of saline solution or of oxalated plasma of 0.62 (table 3). In this concentration, as shown by inspection of the solid curve in chart 1, the apparent average increase in volume of all types of erythrocytes was 30 per cent. It was then assumed, however, that the increased resistance to hemolysis of the other types of erythrocytes was due *entirely* to proportionately smaller increases in volume in oxalated plasma of 0.62 concentration but that an equal (30 per cent) increase in volume would be attained at the respective lower concentrations of plasma causing 50 per cent hemolysis of each type of erythrocyte. By substituting for V_e the value of 30 and for P_e the respective values for the relative osmotic pressure causing 50 per cent hemolysis of the various types of erythrocytes (table 3), the respective theoretical values for b were found by solution of the equation $V_e = [\frac{1\ (100-b)}{P_e} + b] - 100$.

The hypothetic values of b thus found were used, and illustrative curves for the erythrocytes of patients with hemolytic jaundice and hypochromic anemia, respectively, were plotted in broken lines as shown in chart 1. The theoretical value of b for hemolytic jaundice was 69.4; that for hypochromic anemia, 82.9 per cent of V_o. Inspection shows at once that these curves fall outside the limits of the observed data given in table 2 and represented by the vertical lines intersecting the solid curve in chart 1. Similar families of curves could, of course, be plotted by taking any other of the types of erythrocytes as the basis of comparison. The position of the curves with respect to the curve for observed swelling would be different, but some of the curves would fall outside the limits of the observed data.

These considerations clearly indicate that differences in osmotic effects cannot explain the observed differences in resistance to hemolysis. Although slight differences in the percentage increase in volume of the different types of erythrocytes may exist because of slight differences in individual values for b, it appears probable that a given mass of erythrocytes of any of the types studied takes up from a given concentration of diluted plasma very nearly the same amount of liquid. Likewise, from a recent investigation of the osmotic properties of the erythrocytes of four species (sheep, ox, rabbit and man) after conversion into a spherical form without change in volume, Ponder[3] concluded that differences in water content and in the extent to which the erythrocytes behave as "perfect osmometers" play only a minor part in determining differences in susceptibility to hemolysis. Ponder's

observations, however, were made on erythrocytes converted into a spherical form without change in volume by the addition of lecithin. Consequently, the experimental conditions do not necessarily correspond to those obtained when erythrocytes are freely suspended in hypotonic plasma or saline solution.

Whether the discoidal form of the erythrocyte is inherent in the construction of the cell envelop (to use Ponder's [14b] simile, "as a Rugby

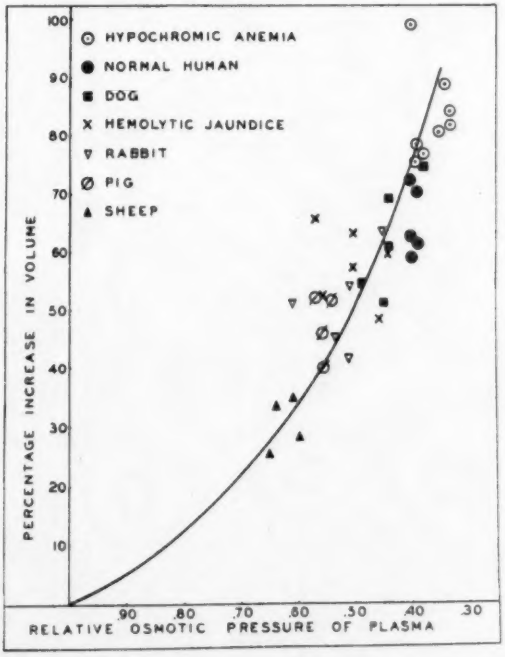

Chart 3.—The percentage increase in discoidal volumes of samples of individual erythrocytes, calculated as a function of their respective *discoidal diameter-thickness ratios,* relative to that of the average sheep erythrocyte. These values are plotted against the respective relative osmotic pressures for mean hemolysis of each sample of erythrocytes. The curve is that shown in chart 1.

football is different from an Association football") or whether the discoidal form is the resultant of forces acting on an envelop of uniform extent, would influence the accuracy of calculations based on Gänsslen's hypothesis. The question cannot at present be definitely answered. Microscopic observations, however, apparently indicate that in swelling the erythrocyte becomes spherical.

It is certain that after the erythrocyte has become spherical a further increase in volume will cause extension or stretching of the cell membrane. If a geometric explanation of differences in susceptibility to hypotonic hemolysis is to obtain, it is necessary to suppose that the release of the cell contents containing hemoglobin is brought about by physical effects on the cell membrane. That physical injury to the membrane may cause a release of hemoglobin, though sometimes denied,[20] has been proved by microdissection[21] and can be easily

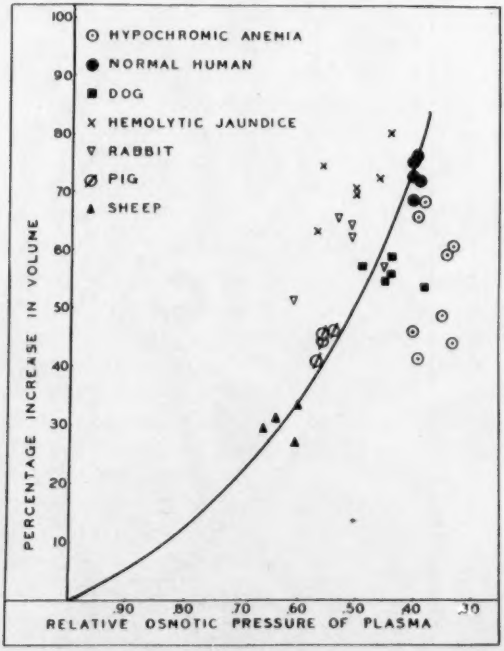

Chart 4.—The percentage increase in discoidal volumes of samples of individual erythrocytes, calculated as a function of their respective *discoidal volumes*, relative to that of the average sheep erythrocyte. These values are plotted against the respective relative osmotic pressures for mean hemolysis of each sample of erythrocytes. The curve is that shown in chart 1.

demonstrated by grinding oxalated blood with fine emery powder in a mortar for a few minutes, with adequate provision for prevention of

20. Rockwood, R.: Physicochemical Aspects of Hemolysis: II. An Ultramicroscopic Study of Hemolysis, J. Lab. & Clin. Med. **10**:19, 1924.

21. Seifriz, W.: The Physical Properties of Erythrocytes, Protoplasma **1**:345, 1927.

heating and evaporation. After centrifugation of the contents of the mortar, the supernatant plasma will be found to contain hemoglobin free from erythrocyte débris. The properties and behavior of the erythrocyte therefore seem to be consistent with a geometric explanation of differences in susceptibility to hypotonic hemolysis.

The difficulties of subjecting Gänsslen's hypothesis to quantitative tests are obvious. It is fully realized that every step in the calculation

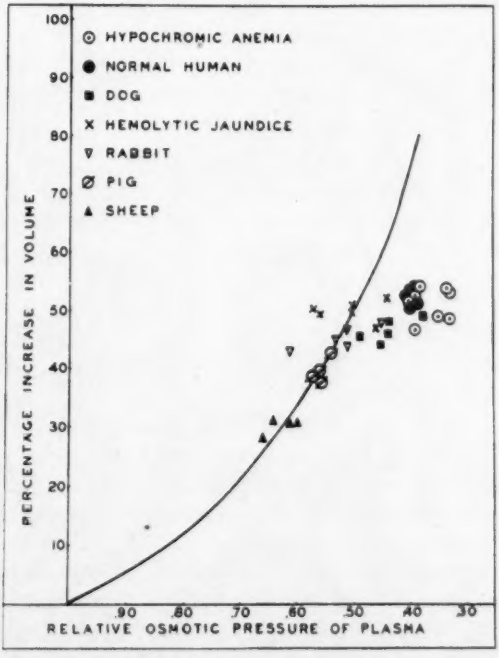

Chart 5.—The percentage increase in discoidal volumes of samples of individual erythrocytes, calculated as a function of their respective *discoidal diameters,* relative to that of the average sheep erythrocyte. These values are plotted against the respective relative osmotic pressures for mean hemolysis of each sample of erythrocytes. The curve is that shown in chart 1.

of the value $\frac{V_s - V_o}{V_o}$ depends on approximations imposed by the experimental conditions rather than on accurate measurement of the erythrocyte. Values for V_o were obtained in oxalated plasma, whereas values for mean diameter (D_o) were obtained in dried smears. Because the precise shape of the erythrocyte is not known, it is obviously impossible to calculate exactly the surface of the erythrocyte at volume

V_o. Therefore, von Boros'[16] assumption of its resemblance to a right cylinder appears to be as satisfactory a method as any of obtaining at least a relative value for the mean corpuscular thickness and hence for the surface of the erythrocyte.

A certain degree of correlation between mean susceptibility to hypotonic hemolysis and any measurement of the erythrocyte is to be expected if differences in its form are responsible for differences in susceptibility to hypotonic hemolysis. Thus, in charts 4 and 5 some correspondence with the curve for the equilibrium volume is observed for the relative percentage increases in volume which might be expected at the point of 50 per cent hemolysis of each *sample* of erythrocytes if such an increase were a function, respectively, of the original discoidal diameter or volume of the erythrocytes. In chart 3, in which the

TABLE 5.—*Calculated Average Percentage Increase in Volume at Relative Osmotic Pressure for Mean Hypotonic Hemolysis*

	Values Relative to Sheep Erythrocytes as Function of				Absolute Values		
Type of Erythrocyte	V_o	D_o	S_o	$D_o : T_o$	$\frac{V_s - V_o}{V_o}$	V_h	P_h
Hypochromic anemia	54.0	51.0	55.6	82.2	80.3	86.0	0.363
Normal human being	72.6	51.9	63.1	64.2	59.5	75.0	0.395
Dog	56.0	46.7	52.1	61.4	57.1	62.3	0.440
Hemolytic jaundice	71.6	49.7	60.6	57.3	51.7	48.0	0.505
Rabbit	60.1	45.0	52.3	50.9	46.1	43.4	0.530
Pig	43.8	39.5	41.6	46.8	42.9	38.5	0.560
Sheep	30.0	30.0	30.0	30.0	27.4	30.0	0.620

V_o, D_o, T_o and S_o are the discoidal volume, diameter, thickness and surface, respectively, of the erythrocytes in isotonic plasma. For convenience the reciprocal of the T:D ratio of Haden[9] has been used. V_h, or $\left[\frac{1(100-51)}{P_h} + 51\right] - 100$, indicates the percentage increase in discoidal volume at P_h. P_h indicates the relative osmotic pressure for mean hypotonic hemolysis.

relative values are based on the discoidal diameter-thickness ratio[22] of the various samples of erythrocytes, the correspondence is much better and seems to be as good as that obtained on the basis of the $\frac{V_s - V_o}{V_o}$ value shown in chart 2. The basis for computation of these relative values was the average sheep erythrocyte considered to have, from inspection of chart 1, an increase in volume of 30 per cent at a relative osmotic pressure of 0.62, the value for 50 per cent hemolysis. It is to be emphasized that, whereas the calculations based on the diameter, volume or diameter-thickness ratio give merely *relative* values here calculated with respect to the average sheep erythrocyte as a base, the expression $\frac{V_s - V_o}{V_o}$ is an attempt at an *absolute* value.

In table 5 the various types of erythrocytes are arranged in the order of increasing average susceptibility to hemolysis. The cor-

22. For convenience the reciprocal of the thickness-diameter ratio of Haden[9] is used.

respondence, both in order and numerically, of the $\frac{V_s - V_o}{V_o}$ values with the average values for the relative osmotic pressure causing mean hemolysis has been pointed out (tables 3 and 5). This order is likewise preserved by the percentage increases in volume relative to the sheep erythrocyte, calculated on the basis of the diameter-thickness ratio. On the contrary, in respect to correlations on the basis, respectively, of original volume, diameter and surface, shown in table 5, there are two notable exceptions to this order which throw weight in favor of the significance of the *form* of the erythrocyte in determining its susceptibility to hypotonic hemolysis. The small discoidal volume of the erythrocyte of hypochromic anemia would place it just above the erythrocytes of the pig in table 5. On the basis of discoidal volume, the erythrocytes of hemolytic jaundice would be classed with normal human erythrocytes; on the basis of discoidal diameter, they would be placed between the erythrocytes of normal man and those of the dog. Correlations based on the discoidal surface of each type of erythrocyte also show that the erythrocytes of hypochromic anemia and those of hemolytic jaundice present exceptions. Placed in order of increase in volume as a function of discoidal surface, the erythrocytes of hypochromic anemia would come below, instead of above, the erythrocytes of normal man; the erythrocytes of hemolytic jaundice would come above instead of below the erythrocytes of the dog.

Thus, when susceptibility of the erythrocyte to hypotonic hemolysis is regarded as a function of the percentage difference between the original discoidal volume and the volume of a sphere of equal surface, the varied susceptibility to hemolysis of the erythrocytes of these different species and pathologic conditions can, to some extent, be anticipated.[14a]

CONCLUSIONS

Our results suggest that differences in the susceptibility of various types of erythrocytes to hemolysis with hypotonic solution of sodium chloride are due largely to differences in form and not to differences in osmotic behavior.

The percentage increases in equilibrium volumes in hypotonic plasma of erythrocytes of widely different susceptibilities to hemolysis do not show significant differences.

Direct microscopic observations indicate that (*a*) hemolysis of a given type of erythrocyte is associated with the assumption of a spherical form in hypotonic plasma and that (*b*) the more susceptible the erythrocyte to hypotonic hemolysis, the less hypotonic the plasma necessary to cause the assumption of a spherical form.

An approximation to the percentage increase in volume necessary to cause hemolysis can be made by calculation of the percentage difference between the volume of the erythrocyte in isotonic plasma (V_o) and that of a sphere of equal surface (V_s).

In correlations of the *relative* degree of susceptibility to hypotonic hemolysis of a series of types of erythrocytes with their respective volume, diameter or surface in isotonic plasma, the erythrocytes of hypochromic anemia and of chronic hemolytic jaundice present exceptions.

When these correlations are made on the basis of the diameter-thickness ratio or when *absolute* values are calculated according to the formula $\frac{V_s - V_o}{V_o}$, the erythrocytes of hypochromic anemia and of chronic hemolytic jaundice do not present these exceptions.

Differences in the time necessary to cause hypotonic hemolysis of different types of erythrocytes may possibly be explained by difference in the percentage increase in volume of the discoidal form necessary to produce the spherical form in hypotonic solution.

RETENTION AND UTILIZATION OF PARENTERALLY ADMINISTERED IRON

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Parenterally administered iron has been used for many years in the treatment of anemia. Stockman,[1] in 1893, reported on the efficacy of this mode of administration and quoted many previous investigators who had found it to be of value, but from his own experience he concluded that a more rapid increase in the hemoglobin content could be obtained by oral administration. He stated, however, that the therapeutic activity of iron when given by this route was evidence that it was actually absorbed and utilized, a point which was being questioned at that time. This method of administration has been used by Witts,[2] by Barlow [3] and Bullock [4] in the anemia of tuberculosis and by Morse [5] in the anemia of infants, as well as by numerous other investigators. All have recognized the fact that the amount of iron administered parenterally must be small because of its toxicity. More recently Heath, Strauss and Castle [6] have reviewed the previous investigations and have presented evidence not only of the effectiveness but of the toxicity of iron when given by this route. They have shown that iron so administered to a group of seventeen patients produced a reticulocyte response as well as a rather rapid increase in the hemoglobin content of the blood and that 32 mg. of iron administered parenterally is equivalent to 1,000

From the Department of Internal Medicine, the State University of Iowa.
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1. Stockman, R.: The Treatment of Chlorosis by Iron and Some Other Drugs, Brit. M. J. **1**:881 and 942, 1893.

2. Witts, L. J.: Treatment of Anemias, Brit. M. J. **1**:100 (Jan. 21) 1933.

3. Barlow, W. J., and Cunningham, R. L.: Effects of Hypodermic Injection on the Secondary Anemia of Chronic Pulmonary Tuberculosis, J. A. M. A. **57**: 1435 (Oct. 28) 1911.

4. Bullock, E. S., and Peters, L. S.: The Use of Hypodermics of Citrate of Iron in the Secondary Anemia of Tuberculosis, J. A. M. A. **57**:1428 (Oct. 28) 1911.

5. Morse, J. L.: The Treatment of Anemia in Infancy with Citrate of Iron Administered Subcutaneously, J. A. M. A. **53**:107 (July 10) 1909.

6. Heath, C. W.; Strauss, M. B., and Castle, W. B.: Quantitative Aspects of Iron Deficiency in Hypochromic Anemia: The Parenteral Administration of Iron, J. Clin. Investigation **11**:1293, 1932.

mg. administered by mouth. In only two of their seventeen patients did the hemoglobin content fail to increase, and the average utilization of the iron in hemoglobin formation in fourteen of the seventeen patients was 96 per cent, with extremes of 69 and 154 per cent. They concluded that the amount of iron given parenterally corresponds closely to the amount of iron gained in the circulating hemoglobin.

We [7] have presented studies showing the retention and utilization of orally administered iron as determined by studies of the iron balance and wish to present similar balance studies of patients receiving iron parenterally.

TABLE 1.—*Clinical Features*

Patient	Age	Sex	Diagnosis	Clinical Features
1	45	F	Hypochromic anemia; hemorrhage	Pale and anemic for eighteen years; menstrual periods always profuse; several severe uterine hemorrhages; biopsy showed only hyperplastic endometritis
2	43	F	Hypochromic anemia; hemorrhage; pregnancy	Profuse menses for several years; one severe uterine hemorrhage and one postpartum hemorrhage; pale since ninth and last pregnancy
3	52	F	Hypochromic anemia; hemorrhage	Pale and weak for four years; symptoms began with severe climacteric bleeding; several profuse hemorrhages from hemorrhoids; dysphagia
4	40	F	Hypochromic anemia, idiopathic (?); pregnancy (?)	No history of excessive loss of blood; eleven pregnancies

TABLE 2.—*Hematologic Data* *

Patient	Hemoglobin, Percentage	Hematocrit Reading, Percentage	Erythrocytes, Percentage	Color Index	Volume Index	Saturation Index	Gastric Acidity	Basal Metabolic Rate
1	55	77	77	0.71	1.00	0.71	0	+10
2	49	63	80	0.61	0.78	0.77	Low	—11
3	39	45	60	0.65	0.75	0.86	0	— 4
4	55	72	73	0.75	0.98	0.76	0	+ 4

* The percentages and indexes are based on the normal values and tables of Osgood (A Textbook of Laboratory Diagnosis, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1935, p. 420).

METHOD

These metabolic studies were carried out on patients with a microcytic hypochromic type of anemia. A brief summary of the clinical and hematologic features is given in tables 1 and 2. The details of the methods employed in these experiments have been given in a previous report.[7a] Three diets were arranged for each patient according to the caloric requirement and were alternated during the period of study. The patients received these diets for a three day period of adjustment

7. (*a*) Fowler, W. M., and Barer, Adelaide P.: Retention and Utilization of Orally Administered Iron, Arch. Int. Med. **59**:561 (April) 1937; (*b*) Retention and Utilization of Small Amounts of Orally Administered Iron, ibid. **59**:1024 (June) 1937. (*c*) Barer, Adelaide P., and Fowler, W. M.: Influence of Copper and a Liver Fraction on Retention of Iron, ibid. **60**:474 (Sept.) 1937.

before observations were begun. The iron balance was then ascertained for a control period in which the intake of iron was from the food alone. This, as well as the subsequent periods during which medicinal iron was administered, was of six days' duration. The intake and excretion of iron for each period were determined, and from these data was calculated the daily iron balance. Complete data for the nitrogen and phosphorus balances were determined for all the patients.

One-tenth gram of green iron and ammonium citrates was administered intramuscularly at daily intervals. The iron content of this preparation was ascertained by analysis of representative samples from each lot, and from this analysis and from the number of intramuscular injections was determined the amount of medicinal iron each patient received. Two patients were given 3 Gm. of iron and ammonium citrates per day by mouth after receiving iron intramuscularly for twenty-four and eighteen days, respectively.

Determinations of the hemoglobin content, made by the Newcomer method, erythrocyte and reticulocyte counts and hematocrit readings were made on alternate days for all the patients.

A portion of the specimen of stool of patient 4 for the second period was lost, so that no balance studies could be made for that period. The patient received the medicinal iron continuously, however, so that the determinations of hemoglobin and erythrocytes were still of value.

RESULTS

The results of the studies of the nitrogen, phosphorus and iron balances are given in table 3, and table 4 presents a summary of the data on the iron retention of each patient. It will be noted in these tables that the retention of iron was much greater during the periods in which intramuscular injections of iron were being given than it was during the control periods. Patient 1 retained a total of 152.1 mg. of iron and received only 139.7 mg. by intramuscular injection, so that all medicinal iron was retained as well as a portion of the dietary iron (table 5). The same feature is true for patient 2, who retained 167.82 mg. of iron, although only 139.7 mg. of medicinal iron was administered. The control period for this patient showed a loss of 5.05 mg. of iron per day, but it is obvious that a portion of the dietary iron was retained in the remaining periods. In patient 3 there was a retention of 303.89 mg. from the administration of 304.8 mg., so that over 99 per cent of the medicinal iron was retained and the diet was apparently just sufficient to keep the patient in balance. Owing to the loss of one specimen for patient 4, the data on iron retention cannot be subjected to analysis.

These results indicate that the entire amount of intramuscularly administered iron is retained by the body.

Iron was administered by mouth to patients 3 and 4 after they had received iron intramuscularly for twenty-four and eighteen days, respectively. Patient 3 received a total of 6,212.4 mg. of iron during two balance periods and retained 2,187.42 mg., a retention of 35 per cent of the amount administered. Patient 4 retained 47 per cent of the orally administered iron during the same length of time. These results are

TABLE 3.—*Nitrogen, Phosphorus and Iron Balances*

Patient	Period	Nitrogen, Gm.			Phosphorus, Gm.			Iron, Mg.			Red Blood Cells, Millions per Cu. Mm.	Hematocrit Reading, Percentage	Hemoglobin, Gm. per 100 Cc.
		Average Daily Intake	Average Daily Excretion	Average Daily Balance	Average Daily Intake	Average Daily Excretion	Average Daily Balance	Average Daily Intake	Average Daily Excretion	Average Daily Balance			
1	1	9.78	9.35	+0.43	1.44	1.20	+0.24	11.89	11.78	+ 0.11	3.83	31.5	7.890
	2	9.79	8.95	+0.84	1.44	1.19	+0.25	22.47	10.85	+ 11.62	4.15	31.0	7.625
	3	9.79	8.66	+1.13	1.45	1.17	+0.28	24.59	10.86	+ 13.73	4.15	33.5	7.800
2	1	9.78	9.90	−0.21	1.44	1.57	−0.13	11.89	16.93	− 5.05	3.98	27.0	7.015
	2	10.41	8.81	+1.60	1.50	1.12	+0.38	24.63	10.58	+ 14.06	3.99	28.0	7.100
	3	10.41	8.49	+1.92	1.49	1.21	+0.28	22.52	8.60	+ 13.92	3.55	32.0	7.275
3	1	9.79	8.89	+0.90	1.45	1.23	+0.22	11.86	14.00	− 2.14	3.01	19.0	5.645
	2	9.83	7.55	+2.28	1.45	1.41	+0.04	24.59	18.72	+ 5.87	3.38	20.0	5.450
	3	9.79	8.54	+1.25	1.44	1.24	+0.20	24.29	8.26	+ 16.03	3.64	21.0	5.450
	4	9.83	8.56	+1.27	1.45	1.38	+0.07	24.59	8.10	+ 16.49	3.63	21.5	5.595
	5	9.83	9.40	+0.43	1.45	1.40	+0.05	24.59	12.33	+ 12.26	3.77	25.0	5.355
	6*	10.11	8.59	+1.52	1.45	1.18	+0.27	517.70	237.10	+280.60	3.86	26.5	6.595
	7*	10.11	9.24	+0.87	1.45	1.76	−0.31	517.70	433.73	+ 83.97	4.47	31.0	7.625
4	1	9.77	9.88	−0.11	1.44	1.30	+0.14	11.59	10.08	+ 1.52	3.62	31.0	7.800
	2	9.80	....	.....	1.45	....	.....	24.56	.....	.....	3.89	29.0	7.015
	3	9.84	9.18	+0.66	1.45	1.17	+0.29	24.60	12.31	+ 12.29	3.87	30.0	7.365
	4	9.85	9.41	+0.44	1.44	1.27	+0.17	24.59	19.12	+ 5.47	4.30	31.0	7.570
	5*	10.14	10.43	−0.29	1.44	1.25	+0.19	517.70	284.08	+233.63	4.43	33.0	8.905
	6*	10.14	10.25	−0.11	1.44	1.40	+0.04	517.70	263.69	+254.01	4.13	35.0	10.940

* The patient received iron and ammonium citrates orally, 3 Gm. per day.

similar to those obtained for a group of ten patients who received the same amount of iron by mouth and in whom the iron retention varied from 14 to 71.4 per cent, with an average retention of 32.6 per cent.[7a] It is apparent, therefore, that patients 3 and 4 reacted similarly to the same amount of orally administered iron as did other patients.

Our results differ from those of other investigators in respect to regeneration of hemoglobin. Both in animals [8] and in human beings [6] it has been reported that iron is used almost quantitatively in hemoglobin formation. The amount of iron that we have injected has been relatively small, but we have shown that it has been retained almost completely. In spite of this retention, there was no regeneration of hemoglobin in three of the four patients, and only an exceedingly slight increase was

TABLE 4.—*Retention of Iron*

Patient	Iron Balance, Mg.						
	Control Period	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6
1	+0.11	+11.62	+13.73				
2	−5.05	+14.06	+13.92				
3	−2.14	+ 5.87	+16.03	+16.49	+ 12.26	+280.60*	+83.97*
4	+1.52	.....	+12.29	+ 5.47	+233.63*	+254.01*	

* The patient was receiving iron and ammonium citrates by mouth.

TABLE 5.—*Total Retention of Iron*

Patient	Total Iron Received in Diet, Mg.	Total Iron Received Intramuscularly, Mg.	Total Iron Retained, Mg.
1	142.64	139.70	152.10
2	143.20	139.70	167.82
3	283.58	304.80	303.89

noted in patient 2. Although the first two patients received iron for only twelve days, it seems that some regeneration should have been apparent within that length of time. Patients 3 and 4 received iron for twenty-four and eighteen days, respectively, with no regeneration of hemoglobin, and the duration of treatment cannot be criticized in these cases.

In order to determine whether the patients were capable of regenerating hemoglobin under more favorable conditions, iron and ammonium citrates was administered orally to patients 3 and 4 in doses of 3 Gm. per day. Under these conditions a prompt and rapid hemoglobin response was obtained. Patient 3 gained 2.27 Gm. of hemoglobin per hundred cubic centimeters of blood in twelve days, an increase of 0.189 Gm. per day. Patient 4 gained 3.37 Gm. during the same length of time,

8. Whipple, G. H., and Robscheit-Robbins, F. S.: Iron and Its Utilization in Experimental Anemia, Am. J. M. Sc. **191**:11, 1936.

which was an increase of 0.28 Gm. per day. This is a more rapid gain than was obtained with the use of the same amount of orally administered iron in previously reported cases.[7a] It indicates that these patients were capable of regenerating hemoglobin under suitable conditions and that the lack of response to iron administered intramuscularly was not due to the patient's inability to form new hemoglobin. The rapidity with which hemoglobin was formed when the iron was given by mouth may indicate that the tissue iron had been restored to normal by the intramuscular injections and as a result the response to the oral administration was more rapid than it would have been had the same amount of iron been given by mouth at the onset of treatment. Hare [9] has reported similarly on a patient who received iron intramuscularly for nineteen days without benefit but who showed immediate and marked improvement when iron and ammonium citrates was given by mouth.

Although the hemoglobin response to iron administered intramuscularly was negligible in all cases, it will be noted that the erythrocyte count and the hematocrit reading increased for all but patient 2. An extremely slight reticulocyte response was obtained, 3.2 per cent for patient 3 being the highest reading. For the other patients the highest values were 1, 1.4 and 1.4 per cent, respectively.

CONCLUSIONS

These results show that iron injected intramuscularly in the form of iron and ammonium citrates is retained by the body. It was expected under these circumstances that hemoglobin regeneration would follow, but this did not occur. That this lack of hemoglobin response is not due to an inability on the part of the particular patient to regenerate hemoglobin is shown by the rapid response of two of the patients who subsequently received iron by mouth. The reports of other investigators have shown that hemoglobin regeneration does ensue, both in animals and in human beings, after the intramuscular or the intravenous injection of iron, and we are at a loss to explain the almost complete absence of response in these patients. The dose which we employed, 0.1 Gm. of green iron and ammonium citrates, is somewhat smaller than that which has been recommended. Heath [6] administered the equivalent of 8 mg. of iron intramuscularly to five patients and noted a slight hemoglobin response within from ten to eighteen days, and when 16 mg. of iron was given to two patients for ten days, the increase in hemoglobin was 3 and 8 per cent, respectively. The average amount of iron which we gave was 12.3 mg. per day. Although it is dangerous to draw extensive conclusions in respect to hemoglobin formation from such a small series

9. Hare, D.: Treatment of the Anemias, Brit. M. J. **1**:100 (Jan. 21) 1933.

of patients, we did not find this amount of iron to be of value in the treatment of anemia, in spite of the fact that all the iron was retained by the body. It has been assumed that an excessive amount of iron may have some stimulating effect aside from its direct use in hemoglobin formation. Such results as we have obtained, when compared with the excellent results reported with 32 mg. of iron administered intramuscularly, may again raise this question. We do not, however, agree with a statement that parenterally administered iron can be quantitatively recovered in new-formed hemoglobin.

SUMMARY

Our results indicate that iron administered intramuscularly is retained by the body, but in the doses here employed it is not utilized in the formation of hemoglobin. The oral administration of iron appears to be more efficient in the treatment of hypochromic anemia.

CRITICAL ANAPHYLACTIC SHOCK

DURING TREATMENT FOR HAY FEVER: RECOVERY AFTER THREE INTRACARDIAC INJECTIONS OF EPINEPHRINE

STANLEY J. JOYCE, M.D.
DETROIT

The tragedy of sudden death due to anaphylaxis is its unnecessary occurrence. A fatality which results from a purely optional treatment is difficult to reconcile; that a patient would have lived had such a procedure been omitted is not a consoling thought. Too often death has been caused by a prophylactic measure intended to protect the patient from some disease which he might have escaped even without treatment, as by the use of antitetanus serum. The fatal treatment may have been given to relieve symptoms of a disease not in itself serious, such as hay fever; or the reaction may have followed an error or accident in treatment. Furthermore, most of these tragedies could have been averted with immediate and adequate care during the reaction.

These reflections are well illustrated in the following case of a reaction due to ragweed antigen, in which death seemed imminent for about thirty minutes. The usual precaution of withdrawing the plunger of the syringe and the prompt application of a tourniquet did not avert the crisis. The situation was saved only after prompt, continuous and heroic action, including three intracardiac injections of epinephrine, the total administration of a large quantity of epinephrine (16 cc. in one and one-half hours) and inhalation of oxygen for asphyxia resulting from acute pulmonary edema.

REPORT OF A CASE

C. K., a Greek aged 40, married, was being desensitized with antigen of short ragweed for fall hay fever associated with severe asthma of ten years' duration. The first treatment of 200 units of pollen[1] (0.1 cc. of 1:1,000 solution) was given on June 4, 1934. After the patient had arrived home a reaction with moderate asthma and urticaria developed, but cleared spontaneously in a few hours. No trouble from gradually increasing doses was then encountered until the ninth

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Whenever used in the text "epinephrine" is construed to mean a solution of epinephrine hydrochloride (1:1,000).

1. A unit of pollen, as used in this text, is the amount of nitrogen extracted from 0.001 mg. of pollen with distilled water. The controversy over dosage of pollen is outside the scope of this paper.

treatment on July 6, when a similar but more severe reaction occurred during an expectant period of waiting at the office. After the application of a tourniquet to the arm above the site of the injection and the hypodermic administration of several small doses of epinephrine the reaction cleared completely in half an hour. Despite great care, similar reactions occurred after the eleventh and fourteenth treatments. During these reactions the patient exhibited marked cardiac irregularity.

Desensitization was then uneventful until the twenty-third treatment, given at 6 p. m. on August 16, when the same dose (0.28 cc. of 1:25 solution) of antigen was administered as for the twenty-second treatment. Withdrawal of the plunger of the syringe did not show blood, but on withdrawal of the needle a small amount of blood appeared at the site of puncture, probably indicating penetration of a vessel and an impending reaction due to backseepage. By the time a tourniquet was adjusted severe asthma had developed. During the brief period taken to fill an already sterile syringe with epinephrine the reaction had progressed to an alarming degree. Epinephrine was immediately injected into both arms, and the patient was placed on a table. His condition rapidly became worse; he exhibited extreme dyspnea, marked cyanosis, failing pulse and loud bubbling râles (marked pulmonary edema). In less than a minute he became unconscious.[2] Evidences of respirations and pulses were absent. The patient stiffened into a generalized tonic convulsion. Without regard to specific location, epinephrine (1 cc.) was given intracardially, and the patient responded slowly. Artificial respiration was instituted. The rescue squad of the fire department was called and arrived within ten minutes to give oxygen. Five and ten minutes after the first intracardiac injection of epinephrine was given a repetition was necessary. Meanwhile small amounts of epinephrine were being injected frequently into the arms, with massage of the sites of injection free from antigen. The indication for another dose was a relapse, with failing or cessation of the pulse and/or respirations. The patient remained unconscious for forty minutes, and the outlook appeared grave. The skin was purple, cold and clammy. The tongue was markedly edematous, completely filling the wide open mouth. When the patient's condition permitted it, the blood pressure was taken and was observed to be 180 systolic and 70 diastolic. The symptoms gradually cleared, and the patient responded irrationally, slapping away the oxygen mask, letting out loud cries, mumbling and tearing at his clothing. When consciousness was regained, he complained of itching of the soles of his feet, due to marked urticaria.

The patient's condition had been so critical that the tourniquet on the arm containing the antigen was not disturbed for fifty minutes and then only in small spurts, until completely released in about fifteen minutes. From 7 to 8 p. m. the patient vomited several times. About 7:15 p. m. he complained of cardiac pain and was given ⅙ grain (8.1 mg.) of morphine sulfate hypodermically, with relief. During the next few hours the pulse rate ranged from 90 to 130, with variable quality and regularity.

Within an hour and a half of the onset of the reaction the patient's condition was sufficiently improved to permit his removal to a hospital for observation. He was apathetic, quiet and weak. At 8:30 p. m. 300 cc. of normal solution of sodium chloride was given intravenously. The temperature was 98.6 F., the pulse rate

2. Mixtures of antigen and epinephrine, as used by Duke,[5] or application of a pressure cuff before an injection of antigen as used by S. W. Insley (The Control of Shock Following Hypodermic Medication, J. A. M. A. **94**:765-767 [March 15] 1930), would likely prevent these reactions.

88 and the respiratory rate 28. A Murphy drip was instituted for twenty-four hours. For the next thirty-six hours the patient continued to have moderate asthma, which was controlled with twelve small doses of epinephrine or atropine and thereafter, when nausea had stopped, with ephedrine given orally. Small doses of morphine were given twice for comfort.

By the next day (August 17) the cyanosis had entirely cleared. There was moderate weakness. The soft tissues of the left side of the chest were emphysematous. The blood pressure ranged around 112 systolic and 84 diastolic (the patient had moderate arteriosclerosis). The maximum twenty-four hour values were as follows: The temperature was 99.6 F., the pulse rate was 110 and the respiratory rate was 38. The minimum twenty-four hour values were as follows: The temperature was 98.6 F., the pulse rate was 72 and the respiratory rate was 26. On the evening of August 18 the patient was discharged from the hospital.

The results of the treatments with ragweed antigen were nil, and the patient was compelled to migrate north because of severe asthma, which yielded to scarcely anything but epinephrine, and then only for brief periods. The patient was seen in July 1936 and was in his usual health.

CRITICAL AND FATAL REACTIONS TO POLLEN

The experience here encountered in the management of a critical reaction to ragweed antigen should prove profitable to other physicians.

Only two deaths and six serious reactions to injections of pollen antigen have been reported. Lamson [3] reported death occurring during treatment with antigen of Bermuda grass which was injected into the area of the deltoid muscle. Two cubic centimeters of epinephrine was given (one dose only; none intracardially). Artificial respiration, dilatation of the rectum and administration of oxygen by the members of the fire department were of no avail, and the patient died within eight minutes.

The other report of a death following injections of pollen extract was found in a chart published by Waldbott [4] listing nine fatal anaphylactic reactions (the rest were due to antiserum). The pollen reaction started one-half minute after the thirteenth injection of ragweed extract, with death in two hours. "No effect from epinephrine" was noted.

A serious reaction to an injection of a pollen-epinephrine mixture was reported by Duke.[5] Coryza, cough and slight asthma developed, followed by convulsions. The patient recovered two minutes after the application of a tourniquet, the injection of epinephrine into the other arm and the rubbing of ice on the chest, back and arms.

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3. Lamson, R. W.: So-Called Fatal Anaphylaxis in Man, with Especial Reference to Diagnosis and Treatment of Clinical Allergies, J. A. M. A. **93**: 1775-1778 (Dec. 7) 1929.

4. Waldbott, G. L.: Prevention of Anaphylactic Shock with Study of Nine Fatal Cases, J. A. M. A. **98**:446-449 (Feb. 6) 1932.

5. Duke, W. W.: New Method of Administering Pollen Extract for Purpose of Preventing Reactions: Subcuticular Method, J. A. M. A. **94**:767-771 (March 15) 1930.

Restall and Burrage [6] reported another serious reaction, which occurred after the sixteenth treatment with ragweed antigen in a boy of 18. With the start of the reaction 12 minims (0.74 cc.) and later 6 minims (0.37 cc.) of epinephrine was given. In about three hours the patient was normal after progressively experiencing drowsiness, weakness, slight twitching and burning of the eyes, symptoms of hay fever, headache, dizziness, blurring of vision, an attack of fainting, chill, tonic convulsions, Cheyne-Stokes respirations, sweating, flushing and amnesia concerning the reaction.

Will Walter [7] reported a case of profound anaphylactic shock starting ten seconds after an injection of ragweed antigen in the same amount as that of a previous dose that had caused no reaction. The patient exhibited violent paroxysms of sneezing, cyanosis, asthma and cough productive of glairy mucus. "The pulse was hardly palpable. The blood pressure dropped to 80. This altogether alarming state lasted about two hours." No mention was made of restoratives.

Waldbott [8] reported three critical reactions following injections of pollen extract. All the patients became dyspneic, cyanotic and unconscious; two became pulseless. One was given 0.5 cc. of epinephrine subcutaneously at once, with a similar dose in three minutes and 1 cc. intramuscularly in another three minutes. The second patient was given 1 cc. of epinephrine at once and a similar dose subcutaneously later. No mention of restoratives was made in the third case.

That no more cases similar to these have been reported is surprising, for their occurrence is of commonplace knowledge. Unwanted notoriety, embarrassment and/or vulnerability of the technic employed probably account for the failure to report these experiences.

USE OF EPINEPHRINE IN OTHER ANAPHYLACTIC REACTIONS

An exhaustive review of the literature disclosed only a few instances of fatal anaphylaxis from all causes in which epinephrine was given intracardially. Three of these were reported by Lamson.[9] One followed the administration of antitetanus serum, another followed an intracutaneous test with ovomucoid (the patient was given "epinephrine even intracardially") and the third followed an intradermal test with

6. Restall, M. M., and Burrage, W. S.: Unusual Type of General Reaction Following Treatment for Hay Fever, New England J. Med. **208**:543-544 (March 9) 1933.

7. Walter, Will: Inoculation Against Hay Fever: An Experience, Warning and Suggestion, J. A. M. A. **75**:670 (Sept. 4) 1920.

8. Waldbott, G. L., and Ascher, M. S.: The Rôle of Accidental Puncture of Veins in the Production of Allergic Shock, Ann. Int. Med. **9**:1232-1239 (March) 1936. Waldbott, G. L.: Systemic Reactions from Pollen Injections, J. A. M. A. **96**:1848-1851 (May 30) 1931.

9. Lamson, R. W.: Sudden Death Associated with Injection of Foreign Substances, J. A. M. A. **82**:1091-1098 (April 5) 1924; footnote 3.

buckwheat. The third patient received epinephrine intravenously, 0.5 cc. at the site of the local reaction and 1 cc. in the opposite arm, and intracardially. In two cases epinephrine was given after the use of hemoplastin.[10] One of these patients "received epinephrine at once and again ten minutes later intracardially." In another case[11] the reaction followed an intracutaneous test with 0.05 cc. of horse serum. Epinephrine (0.3 cc.) was injected into the arm, and further injections of epinephrine both subcutaneously and intracardially were made to "total over 1 cc." Employment of manual artificial respiration and the Drinker respirator was of no avail.

In only three other instances of fatal anaphylaxis can any record of the intravenous administration of epinephrine be found. One followed an injection of diphtheria antitoxin,[12] another followed an intracutaneous test with LePage's glue,[13] and the third,[14] followed an intravenous injection of normal horse serum. In the third case 50 minims (3 cc.) of epinephrine was given intravenously in five divided doses.

Other than as mentioned in the foregoing paragraphs, there were no details as to the number of injections of epinephrine given, the amount or the routes employed.

A number of severe but not critical anaphylactic reactions have been reported. In these cases epinephrine was administered subcutaneously in amounts seldom totaling 3 cc. Numerous reports of fatal anaphylaxis after injection of serum have made no mention of the administration of epinephrine. In one case 20 drops was placed under the tongue, in a number of cases a single dose or several small doses were given subcutaneously and in many cases it was noted that epinephrine was administered, but no further details were cited.

EPINEPHRINE GIVEN INTRACARDIALLY

Intracardiac injections of epinephrine have been given on numerous occasions for other than anaphylactic reactions. Real interest in this pro-

10. DeLee, J. B.: Fatal Anaphylaxis Following Hemoplastin, J. A. M. A. **82**:1564 (May 10) 1924. Neale, A. V.: Acute Anaphylactic Shock: Report of a Fatal Case, Brit. J. Child. Dis. **27**:112-116 (April-June) 1930.

11. Freedman, H. J.: Acute Anaphylactic Shock Following Intracutaneous Test for Sensitivity to Horse Serum: Report of a Fatal Case, New England J. Med. **212**:10 (Jan. 3) 1935.

12. Bullowa, J. M., and Jacobi, Mendel: Fatal Human Anaphylactic Shock, Arch. Int. Med. **46**:306-315 (Aug.) 1930.

13. Cooke, R. A.: Studies in Specific Hypersensitiveness: Constitutional Reactions; Dangers of Diagnostic Cutaneous Test and Therapeutic Injections of Allergens, J. Immunol. **7**:119-146 (March) 1922.

14. Boughton, T. Harris: Anaphylactic Death in Asthmatics, J. A. M. A. **73**:1912 (Dec. 27) 1919.

cedure developed about 1921, although credit is given to Latzko [14a] for administering the first intracardiac injection to a human being in 1904. In the period of clinical trial "it was hailed as a miracle" as well as "a useless and dangerous operation." The procedure "occupied a stage of excited debate,"[15] and skepticism was unreserved. Considerable controversy developed as to whether epinephrine should be given into the pericardial cavity, the cardiac muscle or a specific chamber. Injection into an auricle has obtained most favor. However, time should not be sacrificed in the selection of a site for injection.

Intracardiac injection of epinephrine is now definitely accepted as without an equal in all serious conditions in which there is any possibility of the patient's survival if the emergency can be passed. It is a specific antidote for anaphylactic reactions. Common indications are found in critical states of narcosis, including spinal and other forms of anesthesia, acute pulmonary edema, severe shock from injuries and acute respiratory or heart failure.

No authentic harm has ever been reported as a consequence of intracardial injections in cases of emergency. Petit-Dutaillis [16] reported on over one hundred postmortem examinations in which it was almost impossible to find the intracardiac course of the needle. Large amounts of epinephrine and a number of injections can be given with reasonable impunity in a crisis. Error is more likely on the side of insufficiency. Dennis Crile [17] reported on several cases in which a large quantity of epinephrine was given: from 10 to 20 cc. intravenously and from 5 to 10 cc. intracardially. Paul Champlin [18] gave a 10 cc. dose of epinephrine intracradially to a patient who had collapsed during spinal anesthesia; recovery followed with no ill effects.

COMMENT

The dramatic effects of epinephrine are well known. The literature reveals an unbelievable paucity of reports on the use of the drug in severe and fatal anaphylactic shock. Many of these deaths can be directly charged to failure to use epinephrine at all or adequately. The

14a. Latzko, cited by Bodon, C.: The Intracardiac Injection of Adrenalin, Lancet **1**:586-590 (March 24) 1923.

15. Hyman, A. S.: Resuscitation of the Stopped Heart by Intracardiac Therapy, Arch. Int. Med. **46**:553-568 (Oct.) 1930.

16. Petit-Dutaillis, D.: Intracardiac Injection of Epinephrine, abstr., J. A. M. A. **83**:720 (Aug. 30) 1924.

17. Crile, Dennis W.: Resuscitation, Intracardiac Injections, Surg., Gynec. & Obst. **35**:772-775 (Dec.) 1922.

18. Champlin, Paul B.: Resuscitation by Intracardiac Injection of Epinephrine Chlorid, J. A. M. A. **81**:202-203 (July 21) 1923.

following comment from an article published only a few years ago in *The Journal of the American Medical Association* by an eminent allergist is typical of the general lack of understanding of the adequate use of epinephrine: "However, the value of epinephrine in extreme cases becomes somewhat doubtful if one considers the fact that death could not be prevented in two cases despite the administration of 1 cc. and 1.5 cc. of epinephrine." The statement, common in the literature, "that death occurred before adrenalin could be administered" is an admission that the physician did not have it available for ready use. Even so, in some of these cases life might still have been saved if a supply could have been obtained reasonably soon. Numerous reports of restoration after more than five minutes of cardiac standstill have been recorded.

Undoubtedly there is greater recourse to the use of epinephrine than the literature discloses, yet an appalling condition, nothing short of criminal negligence, exists. All this in spite of the fact that only little mention of authentic harm from its use is recorded, and no ill effects have followed massive doses, even when given intracardially.

There is no standard dose of epinephrine; the requirements of the moment must be the guide. The drug is best given subcutaneously in small doses (fractions of a cubic centimeter) to avoid unpleasant secondary effects and is repeated as necessary. For the more severe reaction larger doses (1 to 1.5 cc.) are indicated. There should be no hesitancy in the use of the intravenous and intracardiac routes, with repetitions even of large doses, as indicated by the response of the patient. Failure of epinephrine in an emergency can often be attributed to insufficient dosage. A liberal quantity of the drug should be available to all physicians at all times for immediate use, and failure to anticipate the need of epinephrine in an emergency is unpardonable.

The site of a parenteral injection should be chosen so that a tourniquet can be applied if necessary. The experience here cited further emphasizes the dangers of self-administration of pollen antigen or of any parenteral treatment by any one unprepared to meet any emergency.

SUMMARY

A critical reaction to ragweed antigen is reported, with recovery after three intracardiac injections of epinephrine (1 cc. each), the subcutaneous injection of .13 cc. of epinephrine in divided doses and the administration of oxygen.

Although of common hearsay, reports of only two fatal and six critical reactions to pollen antigen can be found in the literature, and in none of these cases was epinephrine given intracardially.

Timidity as to the number of injections or quantity of epinephrine to be given either hypodermically or intracardially in the present case would have resulted fatally.

Reports of resort to the intracardiac administration of epinephrine are surprisingly lacking in articles on serious or fatal anaphylactic reactions.

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COPPER AND IRON IN HUMAN BLOOD

V. NORMAL ADOLESCENT CHILDREN FROM 14 TO 19 YEARS OF AGE

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AND

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OMAHA

In a series of analyses previously made in this laboratory normal values for the copper and iron contents of the whole blood of adults were established.[1] It was shown that while the average values for copper were practically the same, irrespective of sex, values for iron and hemoglobin were appreciably lower for women, so that separate standards of hemoglobin values for men and for women were advocated.

In a more recent report [2] values were established for copper, iron and hemoglobin for normal children, ranging from new-born infants to children of 15 years. The results in this series exhibited no sex variations, but the values fluctuated greatly with changes in age, especially in the first year of life. It was suggested that for greater reliability in clinical interpretation a hemoglobin curve is preferable to a single standard for children.

The present study was undertaken to complete the series of normal values for the copper, iron and hemoglobin contents of the blood from birth to the adult stage. It bridges the gap existing in normal figures obtained in this series of studies for persons between 15 years of age and adult ages.[2] This period may be designated as late adolescence or possibly as the preadult stage, and in the present study these terms will be used arbitrarily to refer to the interval between the ages of 14 and 19 years.

This age period is of special interest because it is during this time that the sex differentiation which is apparent in the blood iron values for adults but absent in those for children makes its appearance. This

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1. Sachs, A.; Levine, V. E., and Fabian, A. A.: Copper and Iron in Human Blood: I. Normal Men and Women, Arch. Int. Med. **55**:227 (Feb.) 1935.

2. Sachs, A.; Levine, V. E., and Fabian, A. A.: Copper and Iron in Human Blood: IV. Normal Children, Arch. Int. Med. **58**:523 (Sept.) 1936.

period is likewise of interest in establishing the age at which the values for adults are reached and whether males and females attain these values at the same age.

METHODS

The determinations of iron and copper reported in this paper were made during the period from November 1935 to May 1936.

The normal adolescent boys were from Father Flanagan's Boys' Home, at Boystown, Neb. The normal adolescent girls were from South High School, in

TABLE 1.—*Values for Copper and Iron in Blood of Normal Adolescent Boys*

Name	Age, Years	Red Blood Cells per Cu. Mm.	Copper, Mg. per 100 Cc.	Iron, Mg. per 100 Cc. (Wong)	Iron, Mg. per 100 Cc. (Ash)	Hemoglobin, Gm. per 100 Cc.*	Hemoglobin, %†	Iron Color Index‡
W. H.	14	5,180,000	0.1688	49.82	49.60	14.81	98	0.95
C. O.	14	4,544,000	0.1446	50.26	50.32	15.02	96	1.11
W. H.	14	4,416,000	0.1720	41.64	40.80	11.88	90	0.93
F. S.	14	5,056,000	0.1550	45.06	44.12	13.17	97	0.86
B. O.	14	4,800,000	0.1656	48.40	48.40	14.45	93	1.00
T. M.	15	5,184,000	0.1722	46.46	45.72	13.65	94	0.88
J. H.	15	4,672,000	0.1566	45.84	45.96	13.72	92	0.98
M. T.	15	5,056,000	0.1782	46.96	46.80	13.97	98	0.92
B. U.	15	5,568,000	0.1594	48.20	46.90	14.00	99	0.84
F. L.	16	4,832,000	0.1556	45.04	44.20	13.19	96	0.92
B. R.	16	5,088,000	0.1566	46.50	46.24	13.80	93	0.90
S. R.	16	4,896,000	0.1686	40.46	39.60	11.82	94	0.82
N. E.	16	4,704,000	0.1526	46.42	45.96	13.79	98	0.98
O. T.	16	4,416,000	0.1598	45.90	46.80	13.97	88	1.07
H. N.	16½	4,992,000	0.1494	51.00	51.28	15.31	98	1.02
K. Y.	17	5,440,000	0.1482	50.50	50.00	14.92	101	0.93
H. Y.	17	4,992,000	0.1548	50.86	51.60	15.40	97	1.04
H. G.	17	5,024,000	0.1580	48.36	48.60	14.51	98	0.97
C. U.	17	5,128,000	0.1270	52.42	53.12	15.85	101	1.04
L. N.	18	5,024,000	0.1432	51.00	50.64	15.11	92	1.01
B. C.	18	4,672,000	0.1394	50.20	50.96	15.21	93	1.08
N. E.	18	4,992,000	0.1364	50.75	51.62	15.41	100	1.03
McG.	19	4,640,000	0.1314	49.90	50.64	15.11	94	1.09
Average		4,927,000	0.1545	47.91	47.82	14.26	95	0.97

* Hemoglobin values were determined from the iron content of the blood obtained by the use of the Butterfield factor—iron equals 0.335 per cent of the hemoglobin molecule (Butterfield, E.: Ztschr. f. physiol. Chem. **62**: 173, 1909).

† The percentages of hemoglobin were determined with the Dare hemoglobinometer.

‡ The iron color index [1] equals $\frac{\text{Mg. of iron in 100 cc. of blood}}{\text{First two figures of red cell count}}$

Omaha. All were in a good state of health, and the red cell, white cell and differential white cell counts were within normal limits. For all the girls who had reached the age of development characterized by the onset of the menstrual cycle, the sample of blood was drawn in every case in the intermenstrual period to eliminate any possible altering effect of this physiologic process on the blood iron or copper. One investigator, Sarata,[3] has claimed that the copper value varies greatly with the menstrual phases. Work done in this laboratory

3. Sarata, U.: Studies in Biochemistry of Copper: VI. Copper in Relation to Menstruation and Pregnancy, Jap J. M. Sc., II, Biochem. **3**:1 (Feb.) 1935.

that is soon to be published indicates that in the subjects studied there was no evident relation between the copper content of the blood and the menstrual cycle except when the flow was excessive and the loss of iron was marked.

Blood counts were made with standardized pipets and counting chambers for blood drawn from the lobe of the ear.

Samples of venous blood were taken from the basilic vein, platinum needles being used. The syringes were rinsed in water free from iron and copper, wrapped in towels and sterilized in an autoclave.

TABLE 2.—*Values for Copper and Iron in Blood of Normal Adolescent Girls* *

Name	Age, Years	Red Blood Cells per Cu. Mm.	Copper, Mg. per 100 Cc.	Iron, Mg. per 100 Cc. (Wong)	Iron, Mg. per 100 Cc. (Ash)	Hemoglobin, Gm. per 100 Cc.	Hemoglobin, %	Iron Color Index
K. O.	14	5,056,000	0.1582	43.42	44.24	13.21	97	0.87
D. A.	14	4,576,000	0.1360	46.60	47.04	14.04	94	1.02
W. L.	14	4,704,000	0.1348	46.26	46.94	14.01	96	0.99
B. R.	14	4,096,000	0.1320	42.90	43.00	12.84	87	1.05
R. C.	14	4,320,000	0.1460	45.32	45.20	13.49	89	1.05
D. A.	15	4,320,000	0.1380	44.10	45.20	13.49	88	1.05
M. C.	15	4,864,000	0.1334	45.94	46.24	13.80	91	0.95
P. O.	15	4,672,000	0.1430	44.20	44.20	13.19	91	0.95
H. N.	15	5,120,000	0.1194	47.10	47.48	14.17	99	0.92
W. S.	15	4,928,000	0.1264	49.82	50.32	15.04	97	1.02
K. O.	15	4,704,000	0.1400	47.04	47.96	14.31	98	1.02
W. L.	16	4,736,000	0.1350	41.60	42.32	12.63	90	0.89
D. V.	16	4,864,000	0.1564	46.86	46.60	13.91	93	0.96
K. A.	16	4,544,000	0.1302	46.24	46.24	13.80	93	1.02
B. U.	16	4,352,000	0.1354	47.80	48.28	14.41	86	1.11
S. I.	16	4,608,000	0.1336	42.40	43.24	12.91	84	0.93
H. R.	16	4,864,000	0.1502	48.80	49.68	14.83	92	1.02
B. E.	16	4,096,000	0.1442	42.12	42.12	12.57	87	1.02
V. L.	16	3,936,000	0.1436	44.42	44.68	13.34	83	1.13
L. N.	16	4,352,000	0.1180	45.16	45.20	13.49	95	1.04
K. L.	17	4,576,000	0.1582	43.20	43.48	12.98	86	0.95
H. L.	17	4,800,000	0.1350	46.96	47.20	14.09	96	0.98
F. L.	17	4,192,000	0.1370	44.98	46.80	13.97	93	1.12
McG.	17	4,736,000	0.1332	43.00	42.32	12.63	90	0.89
W. I.	18	4,672,000	0.1302	41.86	42.76	12.76	86	0.91
O. A.	18	5,216,000	0.1352	46.72	46.94	14.01	100	0.90
O. B.	18	4,640,000	0.1442	46.46	47.23	14.09	98	1.02
O. B.	18	4,544,000	0.1482	42.40	42.56	12.70	89	0.93
C. R.	18	4,864,000	0.1486	46.22	46.52	13.89	90	0.96
Average		4,622,000	0.1387	45.17	45.58	13.61	91	0.99

* See footnotes for table 1.

Special precautions were taken to obtain pure reagents, free from copper and iron. Acids, alkalis and water were redistilled from glass and were tested at frequent intervals for contamination.

The procedure used for the determination of copper was an iron precipitation modification of the method devised by McFarlane,[4] the reagent used being sodium diethyldithiocarbamate, described by Callan and Henderson.[5]

4. McFarlane, W. D.: Application of the Sodium Diethyldithiocarbamate Reaction to the Micro-Colorimetric Determination of Copper in Organic Substances, Biochem. J. **26**:1022, 1932.

5. Callan, T., and Henderson, J. A. R.: New Reagent for Colorimetric Determination of Minute Amounts of Copper, Analyst **54**:650 (Nov.) 1929.

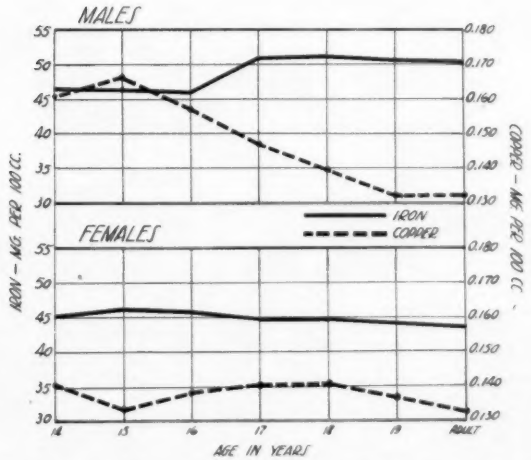

Chart 1.—Curves showing copper and iron values for boys and girls between the ages of 14 and 19 years. The normal averages for adults are included for comparison.

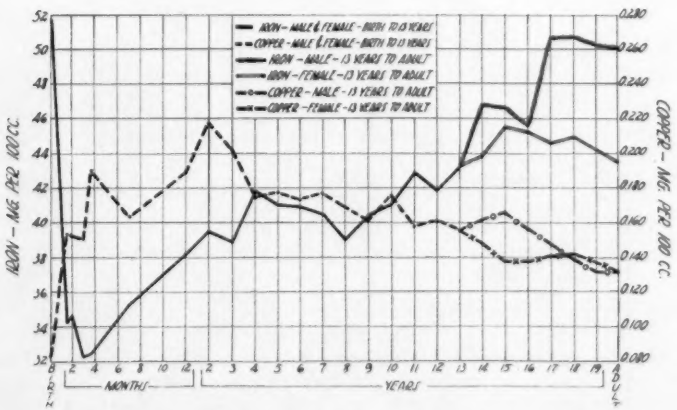
IRON – MALE & FEMALE – BIRTH TO 13 YEARS
COPPER – MALE & FEMALE – BIRTH TO 13 YEARS
IRON – MALE – 13 YEARS TO ADULT
IRON – FEMALE – 13 YEARS TO ADULT
COPPER – MALE – 13 YEARS TO ADULT
COPPER – FEMALE – 13 YEARS TO ADULT
IRON – MG. PER 100 CC.
COPPER – MG. PER 100 CC.
MONTHS
YEARS
BIRTH
ADULT

Chart 2.—Curves showing copper and iron values for males and females from birth to the adult state. These averages include all figures reported in this and in previous papers in this series.[1, 2]

For the determinations of the iron content two methods were used which served as a check one on the other.

Details of the method for determining the copper values [1] as well as the two methods for determining the iron values [6] have previously been described.

TABLE 3.—*Averages of Blood Values for Fifty-Two Normal Boys and Girls Listed in Tables 1 and 2*

Boys	Average	Ranges
Copper, mg. per 100 cc.	0.1545 ± 0.0088*	0.131-0.178
Iron, mg. per 100 cc. (both methods)	47.865 ± 2.165	39.60-53.12
Hemoglobin, Gm. per 100 cc.	14.26 ± 0.608	11.82-15.85
Red cells per cu. mm.	4,927,000	4,416,000-5,568,000
Iron color index	0.97	0.82-1.11
Girls		
Copper, mg. per 100 cc.	0.1387 ± 0.0067	0.118-0.158
Iron, mg. per 100 cc. (both methods)	45.375 ± 1.44	41.60-50.32
Hemoglobin, Gm. per 100 cc.	13.61 ± 0.412	12.57-15.04
Red cells per cu. mm.	4,622,000	3,936,000-5,216,000
Iron color index	0.99	0.87-1.13

* This is the probable error of distribution. Thus, there is a fifty-fifty chance that the copper content of normal whole blood for this age period will fall somewhere within the range between average plus probable error and average minus probable error.

TABLE 4.—*Average Values for Copper, Iron and Hemoglobin in Blood of Normal Adolescent Boys and Girls*

	Age, Years	Red Blood Cells per Cu. Mm.	Copper, Mg. per 100 Cc.	Iron, Mg. per 100 Cc. (Wong)	Iron, Mg. per 100 Cc. (Ash)	Hemoglobin, Gm. per 100 Cc.
Boys	14	4,799,000	0.1612	47.04	46.65	13.87
	15	5,120,000	0.1666	46.87	46.35	13.84
	16	4,821,000	0.1571	45.89	45.68	13.65
	17	5,146,000	0.1470	50.54	50.83	15.17
	18	4,896,000	0.1397	50.65	51.07	15.24
	19	4,640,000	0.1314	49.90	50.64	15.11
Girls	14	4,550,000	0.1412	44.90	45.28	13.52
	15	4,768,000	0.1334	46.37	46.90	14.00
	16	4,484,000	0.1385	45.04	45.48	13.54
	17	4,576,000	0.1408	44.54	44.95	13.42
	18	4,787,000	0.1413	44.73	45.20	13.49

In every case the sample of blood was drawn in a preabsorptive period, at noon, just before lunch. The time is specified because Rabinowitch [7] has shown that the hemoglobin content varies somewhat at different periods of the day.

6. Fabian, A. A.; Sachs, A., and Levine, V. E.: Comparison of Wet and Dry Ashing Methods for Determining Blood Iron, Proc. Soc. Exper. Biol. & Med. **32**: 662 (Jan.) 1935.

7. Rabinowitch, I. M.: Variations of the Percentage of Hemoglobin in Man During the Day, J. Lab. & Clin. Med. **9**:120, 1923.

COMMENT

The period of adolescence is one of instability and adjustment. It is the period of transition from childhood to the adult state, and it is marked by many important physiologic changes. The blood picture based on the iron, hemoglobin and copper contents for boys and girls ranging in age from 14 to 19 years likewise shows a transition from childhood to the adult state. These data exhibit some variation among children within the same yearly age groups, but the averages point to some definite trends.

It was noted in the paper on normal children [2] that up to the fourteenth year of life there was little or no difference in the copper and iron values for boys and girls of any given age. In the preadult group reported on in the present paper, however, a definite differentiation is seen which is based on sex as well as on age. It appears that between the fourteenth and the sixteenth year of life the values for iron are only slightly higher for boys than for girls. Between the ages of 16 and 17 years, however, the iron picture for boys changes rapidly from 45 mg. per hundred cubic centimeters to the men's average of 50 mg. per hundred cubic centimeters. The figure for girls, on the other hand, at 14 years equals the mode for iron of women, which is 45 mg. per hundred cubic centimeters and remains rather constant at that average.

The red cell counts reflected in a curve do not exactly parallel the iron and hemoglobin values, but they are consistently higher for boys.

The figures for copper compared with those for adults are seen to be higher in children.[2] These diminish during the adolescent period until those for boys reach the level for men at about 18 years of age. In girls the copper level for women is reached at about the fourteenth or fifteenth year of life. This average copper value for adults, which is the same for men and women, has previously been established at 0.132 mg. per hundred cubic centimeters of blood.[1]

It seems, on the basis of the iron and copper values, that girls reach maturity at a younger age than boys. The results of this investigation establish maturity in girls at 14 or 15 years and in boys at 17 or 18 years of age. Grigorowa [8] has shown that girls begin to show signs of maturity from two to three years earlier than do boys, basing the stages of development on physical signs, such as the development of the breasts, pubic and axillary hair and changes in the voice. Topper and Mulier,[9] in a study of the basal metabolism of normal boys and girls, have shown a definite increase in metabolism in early puberty followed

8. Grigorowa, O.: Blood Picture During the Pubertal Period, Ztschr. f. d. ges. Anat. (Abt. 2) **15**:24 (Nov. 26) 1929.

9. Topper, A., and Mulier, H.: Basal Metabolism of Normal Children: The Puberty Reaction, Am. J. Dis. Child. **43**:327 (Feb.) 1932.

by a fall after puberty has been established. The rise was found to occur from one to two years earlier in girls than in boys. They stated that "this increase coincides with the physiologic age rather than with the chronological age, and occurs earlier in girls than in boys, coincident with their earlier pubescence." Holt and Howland [10] have cited figures to show that boys and girls grow at approximately the same rate up to the time of puberty; the girls pass the boys during the twelfth and thirteenth years, but the boys then pass the girls at the fourteenth and fifteenth years.

Several investigations of hemoglobin and red cell contents of the blood of adolescent children are reported in the literature. Borchers [11] has stated that in boys the red blood cell and hemoglobin values for adults are attained at 18 years of age. Williamson,[12] after a large series of determinations, made by a spectrophotometric method, has reported that hemoglobin values from birth to the fifteenth year are almost identical for the two sexes. From the sixteenth year on, however, he found that hemoglobin values are considerably lower for females. This agrees well with the findings in the present study as well as with those in the previous report in this series on normal children,[2] although Williamson's values are higher. According to Osgood,[13] however, Williamson's figures are generally recognized as being too high, and he has advocated deducting 10 per cent from them. If this is done they agree well with the hemoglobin values based on iron determinations obtained in the present study. Osgood [13] established normal hematologic standards for a large series, reporting red cell counts, hemoglobin values, color indexes, cell volumes, volume and saturation indexes, reticulocyte counts, leukocyte and differential counts and sedimentation rates. He has reported that the concentration of hemoglobin increases at the same rate for the two sexes until the age of 14, when the values for boys increase more rapidly, quickly reaching the values for adults. This more rapid increase in the hemoglobin value in the boys reported on in his charts shows trends similar to those observed in the present study.

One or two investigators have observed that children from orphanages and institutions show lower figures for hemoglobin than those of

10. Holt, L. E., and Howland, John: Holt's Diseases of Infancy and Childhood, ed. 10, revised by L. E. Holt Jr., and R. McIntosh, New York, D. Appleton-Century Company, Inc., 1936, pp. 21-22.

11. Borchers, J.: Das rote Blutbild gesunder jugendlicher männlichen Geschlechtes im Alter von 13 bis 20 Jahren, Folia haemat. **54**:387, 1936.

12. Williamson, C. S.: Influence of Age and Sex on Hemoglobin: A Spectrophotometric Analysis of Nine Hundred and Nineteen Cases, Arch. Int. Med. **18**: 505 (Oct.) 1916.

13. Osgood, E. E.: Normal Hematologic Standards, Arch. Int. Med. **56**:849 (Nov.) 1935.

similar age from private homes or families. This is a valid objection to the study of children from institutions where the health and food requirements are neglected through mismanagement. However, the boys included in this study were all in a good state of health, and the institution from which they came was well managed and free from political influence. Furthermore, Osgood [13] has stated that results for persons of different social classes used in his study, including children from grade schools, orphan asylums, homes for infants and physicians' families, showed no significant differences.

SUMMARY

Values for the copper, iron, hemoglobin and red cells of the blood were determined for a series of normal boys and girls ranging in age from 14 to 19 years.

The average copper content of whole blood was found to be 0.1545 ± 0.0088 mg. per hundred cubic centimeters for boys and 0.1387 ± 0.0067 mg. for girls.

The average iron content of whole blood was found to be 47.865 ± 2.165 mg. per hundred cubic centimeters for boys and 45.375 ± 1.440 mg. for girls.

The average hemoglobin content of the blood was 14.26 ± 0.608 Gm. per hundred cubic centimeters for boys and 13.61 ± 0.412 Gm. for girls.

The average red cell count was 4,927,000 per cubic millimeter for boys and 4,622,000 for girls.

In an earlier study of children it was noted that the iron and hemoglobin values gradually increased after 3 months of age up to the age of 14 years. The averages were the same for boys as for girls.[2] The present study shows that by the fourteenth year of life the values for both sexes are equivalent to the average value for women. In girls after the fourteenth year the values for iron and hemoglobin become rather constant. The figures for boys, on the other hand, increase only slightly between the ages of 14 and 16 but rise sharply after the sixteenth year, to reach the average value for men by the seventeenth year. It seems, therefore, that differences in the values for iron and hemoglobin due to sex become apparent after the age of 16 years.

The iron and copper values for women were reached by the girls by the fourteenth or fifteenth year, whereas the boys did not attain the values for men until the seventeenth or eighteenth year. This is in accord with other evidences of earlier maturity in girls.

Mr. W. A. Dwyer, of the Department of Mathematics, Creighton University, made the statistical analysis of our data.

SYMPATHECTOMY FOR PERIPHERAL VASCULAR DISEASE

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CHICAGO

A number of arguments have been brought forward against the use of sympathectomy in the treatment of peripheral circulatory disturbances. The purpose of this communication is to examine the validity of these objections in the light of personal experience. Fifty patients have been subjected in my clinic to one hundred and twenty-six sympathectomies (table 1). However, the data for only twenty-four

TABLE 1.—*Indications for Sympathectomy in Peripheral Circulatory Disturbances*

Diagnosis	Total Number of Patients	Number of Patients Operated On*	Indications
Raynaud's phenomena.....	25	6 (15)	Lack of marked structural changes in the vessels; absence of sclerodactylia
Buerger's disease.....	125	10 (21)	Definite collateral reserve; absence of acute inflammation or arteriolar destruction; poor response to conservative treatment
Poliomyelitis.....	25	3 (9)	Moderate paralysis limited to one extremity; evidence of vasospastic phenomena; age preferably between 6 and 10 years
Reflex dystrophy (causalgia, traumatic vessel spasm and Sudeck's atrophy)	5	5 (5)	Severe involvement; resistance to physical therapy; exaggerated vasomotor responses
	180	24 (50)	

* The figures in parentheses indicate the number of patients operated on up to Sept. 1, 1936. For a study of the end-results only those patients have been included who have gone through one or two winters. Study of the group recently operated on, however, has helped to clarify indications and technic.

of these patients, with forty-six sympathectomies, have been used for the evaluation of results, as these patients have been followed for one year or more since operation, the longest period of observation being seven years. Study of the patients more recently operated on has served only to clarify the indications and lead to modifications of the technical procedures.

In the main, four arguments are brought forward against sympathectomy: 1. The peripheral circulation, although temporarily modified after the operation, returns to a preoperative level within from sixteen to twenty-one days. 2. Permanent sympathetic denervation of

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From the Department of Surgery, the University of Illinois College of Medicine, and St. Luke's Hospital.

an extremity is impossible, as the fibers will regenerate and restore continuity with the vessels. 3. The diseases for which the operation is undertaken are not diseases of the vasomotor system. 4. The clinical benefit derived from these operations is often slight and sometimes negligible.

1. RETURN OF THE PERIPHERAL CIRCULATION TO THE PREOPERATIVE LEVEL

The first argument, namely, that the peripheral circulation returns in a short time to the preoperative level, has been maintained by Johnson and his co-workers.[1] They showed in careful studies on several sympathectomized patients that the pulse volume of the fingers, as measured with Johnson's plethysmograph, returns to the preoperative level in a short time. They also found evidence that the vessels react to direct application of heat by vasodilatation. These findings are important, as they show that, just as in the experimental animal, vascular tonus, or the tonus of the smooth muscle of the vessels, is regained after a short initial period of vasodilatation. While this phenomenon was registered as early as 1874 by Goltz and Freusberg for the experimental animal,[2] it was felt for a while that in man a permanent loss of vascular tonus results after sympathectomy.

The observations which my colleagues and I have made indicate, however, that in spite of a recovery of vascular tonus, the peripheral circulation is far from what it was before sympathectomy. The vessels do react to direct application of heat and cold (fig. 1) and they also react to the metabolic requirement of the tissues, because reactive hyperemia can be readily produced after arterial occlusion in the sympathectomized or in the completely denervated extremity. But, being deprived of vasomotor influences, these vessels are freed of a number of important extrinsic and intrinsic stimuli which come continuously or intermittently over the efferent sympathetic pathways. Thus cooling or pinching the body, pain, fright or anger cannot produce vasoconstriction in the sympathectomized extremity[3] (fig. 2), nor will heating the body[4] or the production of fever with typhoid vaccine[1a] produce

1. (*a*) Johnson, C. A.; Scupham, G. W., and Gilbert, N. C.: Studies on Peripheral Vascular Phenomena: II. Observations on Peripheral Circulatory Changes Following Unilateral Cervical Ganglionectomy and Ramisectomy, Surg., Gynec. & Obst. **55**:737, 1932. (*b*) Johnson, C. A., and Davis, Loyal: Paper presented at the meeting of the Central Society for Clinical Research, Chicago, Nov. 7, 1936.

2. Goltz, F., and Freusberg, A.: Ueber gefässerweiternde Nerven, Arch. f. d. ges. Physiol. **9**:174, 1874.

3. Stürup, G.; Bolton, B.; Williams, D. J., and Carmichael, E. A.: Vasomotor Responses in Hemiplegic Patients, Brain **58**:456, 1935.

4. Lewis, T., and Landis, E. M.: Some Physiological Effects of Sympathetic Ganglionectomy in the Human Being and Its Effect in a Case of Raynaud's Malady, Heart **15**:151, 1930.

vasodilatation. The normal vascular tree is in constant motion, regulating temperature and blood pressure, but it can be easily shown that the diseased vascular tree is more seriously affected by these vasomotor impulses because it is narrower or more sensitive. A study of the course of peripheral vascular disease reveals that nothing benefits the patient more than rest in bed and continuous mild heat. A draft, a chill or an emotional upset readily reflects itself on the state of the peripheral circulation. Sympathectomy for these diseased and inflamed vessels means rest from central or reflex stimuli, which to my mind play an important rôle in regulating blood supply.

It must also be emphasized that a diseased vessel, such as a thrombosed artery in Buerger's disease, in itself is responsible for maintaining spasm of the collateral vessels. In an article entitled "Reflex Dystrophy of the Extremities" I [5] have traced this spinal reflex as going through a sensory pathway to the spinal cord and emerging as a sympathetic efferent stimulus through the anterior roots (fig. 3). Sometimes it is

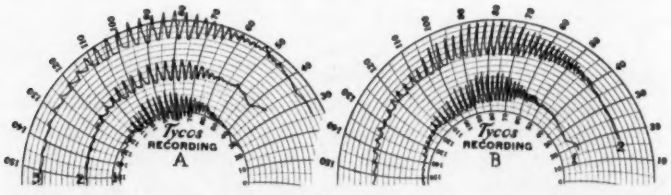

Fig. 1.—The effect of cold, heat and arterial occlusion on the vascular bed of the sympathectomized limb. *A*, Mrs. E. V., aged 27 years, had been suffering from Raynaud's disease. Preganglionic sympathectomy had been performed on the left side five days previously. *1* shows the control curve, *2*, the curve after five minutes in water at 15 C. and *3*, the curve after five minutes in water at 40 C. Note the vasoconstriction due to cold and the vasodilatation due to heat. *B*, *1*, control curve and, *2*, after two minutes of constriction with 200 mm. of mercury during the first minute of release. Each spike denotes the change of volume with each beat. The height of the spikes and the shift of the oscillometric curve to the right indicate the state of peripheral resistance. These charts illustrate that even as early as five days after sympathectomy the circulation is controlled by direct response to the environmental temperature. The reactive hyperemia after arterial occlusion is marked and indicates that metabolic products accumulating during ischemia can produce a further increase in blood flow even during the immediate "maximal" vasodilatation which occurs in the first few days after sympathectomy.

possible to interrupt the afferent side of the reflex by excising the focus of irritation. Thus, in one patient the excision of a thrombosed axillary vein and in another the stripping of an iliac vein due to old lymphangitis and periphlebitis promptly relieved the vasomotor and trophic phe-

5. de Takáts, G.: Reflex Dystrophy of the Extremities, Arch. Surg. **34**:939 (May) 1937.

nomena. When these exaggerated vasomotor and nutritional reflexes are allowed to persist for a certain length of time, definite nutritional disturbances, such as osteoporosis, muscular atrophy, stiffness of joints and sclerosis of connective tissue, develop and are not always reversible.

In most patients suffering from peripheral vascular disease local segmental excision of the irritating focus is impossible. This procedure has been advocated by Leriche,[6] but massive arterial resections can seldom be complete. Recently Clute [7] performed excision for localized arteritis, with striking improvement in circulation. In the majority of cases the interruption of the afferent arc will not be feasible. Sympa-

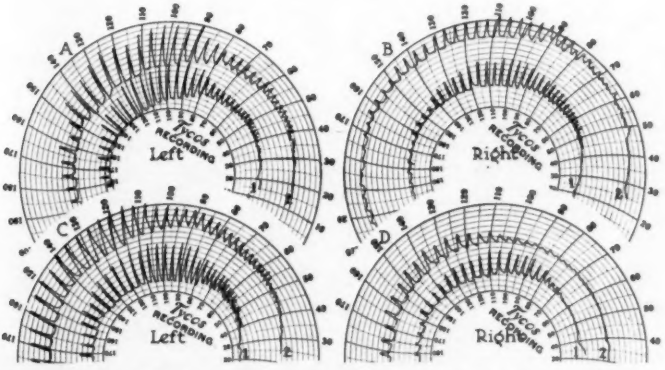

Fig. 2.—The effect of pain and cold on the circulation of the sympathectomized limb in H. M., a 29 year old woman suffering from a reflex dystrophy following mild trauma to the left foot. Left lumbar sympathectomy had been performed two months previously. Graphs *A* and *B* show the effect of pain on the circulation of the left sympathectomized limb as compared with that on the circulation of the right control limb. Pain was induced by injecting 0.4 cc. of 1:1,000 solution of histamine intradermally. While there is no appreciable difference in the sympathectomized limb after the painful stimulus, there is a definite vasoconstriction in the control limb. Note especially the diminution in the height of the spikes at 80 mm. of mercury. In graphs *C* and *D* the combined effect of cold, surprise and anger are demonstrated in the same patient. Both hands were immersed in ice-water for one minute; after the oscillometer was started an ether spray was directed against the area behind the ears, taking the patient by surprise. This combination of stimuli produced slight vasoconstriction in the sympathectomized limb, owing perhaps to an epinephrine effect; but the control side showed a marked increase in peripheral resistance. The pulse waves became small at 100 mm. of mercury, whereas the control showed similar oscillations at 70 mm. of mercury.

6. Leriche, R., and Fontaine, R.: Conditions nécessaires, résultats et technique de l'artériectomie, Presse méd. **43**:1953 (Dec. 4) 1935.

7. Clute, H. M.: Acute Arterial Obstruction from Arteritis, New England J. Med. **214**:137 (Jan. 23) 1936.

thectomy interrupts the efferent arc, and the beneficial results in Buerger's disease and in reflex dystrophies, such as traumatic osteoporosis, Sudeck's atrophy, causalgia and stump neuroma, are at least partly due to the interruption of this spinal reflex.

On the basis of these findings one must admit the beneficial effect of permanent vasomotor palsy on the impaired peripheral circulation. In addition, Hick and I [8] have recently reported another finding which points to an improvement in circulation after sympathectomy. The oxygen saturation of the venous blood, taken from the femoral or

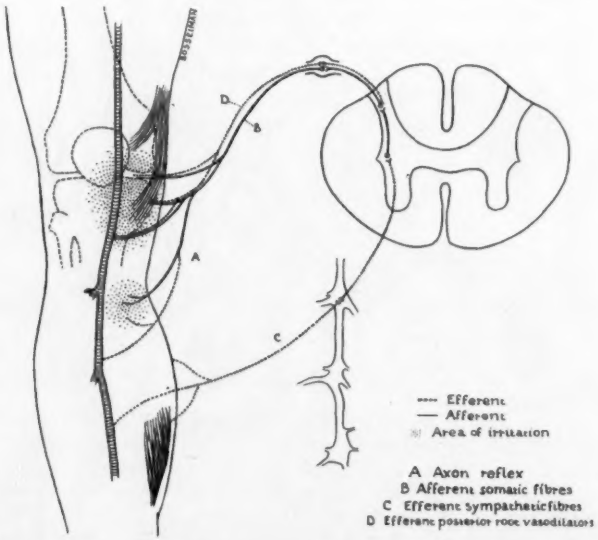

Fig. 3.—The pathway of a spinal sensory-sympathetic reflex operating in certain vasomotor and nutritional disturbances. This reflex is reponsible for shutting down the collateral vessels in acute arterial occlusion (de Takáts, G.: Acute Arterial Occlusions of Extremities, Am. J. Surg. **33**:60 [July] 1936), but it also operates in the posttraumatic reflex dystrophies as a result of a slow continuous stimulus, producing vasodilatation, edema and osteoporosis.[5]

cubital vein, rises after the operation (table 2). The rise does not occur if patients with advanced involvement and with no capacity for collateral reserve are subjected to operation. The rise is marked if there are only slight organic changes or none at all in the vessels, as in cases of early Raynaud's disease or reflex dystrophy. This finding

8. Hick, F. K., and de Takáts, G.: The Value of Sympathectomy in the Treatment of Peripheral Vascular Disease, to be published.

is direct evidence that the supply of oxygen to the tissues is increased after sympathectomy, because the venous-oxygen content reflects the oxygen tension in the tissues, provided arterial oxygen saturation is normal. When the venous oxygen saturation does not rise, the clinical results are poor. The vascular bed in these patients is fixed and is not capable of dilatation. The detection and elimination of these patients by preoperative tests will be discussed later.

2. REGENERATION OF SYMPATHETIC FIBERS

The second important argument against sympathectomy is the regeneration of sympathetic fibers and the restoration of their functional

TABLE 2.—*The Effect of Sympathectomy on Venous Oxygen Content and Saturation* *

Case No.	Initials	Diagnosis	Side	Before Operation: Oxygen Content, Vol. %	Before Operation: Oxygen Saturation, Vol. %	Before Operation: Oxygen Capacity, Vol. %	Two Weeks After Operation: Oxygen Content, Vol. %	Two Weeks After Operation: Oxygen Saturation, Vol. %	Two Weeks After Operation: Oxygen Capacity, Vol. %	Several Months After Operation: Oxygen Content, Vol. %	Several Months After Operation: Oxygen Saturation, Vol. %	Several Months After Operation: Oxygen Capacity, Vol. %
1	S. L.	Buerger's disease	L	11.75	61.4	.....	8.46	45.8	.....	9.02	48.4	.....
			R	6.93	36.3	.....	8.85	47.5	.....	9.53	50.9	.....
						19.10			18.46			18.70
2	F. N.	Buerger's disease	L	11.63	62.9	.....	12.68	77.4	.....	11.90	79.0	.....
			R	.....	....	.....	.....	....	.....	6.62	44.0	.....
						18.48			16.36			15.05
3	J. G.	Buerger's disease	L	16.00	83.7	.....	.....	....	.....	15.90	90.8	.....
		Arms	R	14.90	77.4	.....	.....	....	.....	15.20	85.7	.....
			L	.....	....	.....	10.92	62.4	.....	.....	....	.....
			R	.....	....	.....	12.66	72.4	.....	.....	....	.....
4	A. J.	Raynaud's disease	L	7.87	42.5	.....	15.86	83.0	.....	10.92	60.4	.....
		Arms	R	.....	....	.....	13.60	73.6	.....	12.74	70.4	.....
		Legs	L	9.88	46.7	.....	.....	....	.....	8.52	58.4†	.....
			R	7.92	58.4	.....	.....	....	.....	11.05	76.2	.....
						16.98			19.10			18.06

* In patients who show poor clinical results the oxygen saturation does not rise after sympathectomy (in case 1, both lower extremities; in case 2, the right lower extremity). In patients who still show a capacity for vasodilatation and in whom favorable results have been obtained, the oxygen saturation rises and remains high after sympathectomy.

† On the side not operated on.

activity. In 1935 Cuthbert and I,[9] studying the effect of section of the splanchnic nerve on the sugar tolerance of dogs, stated that regeneration of the splanchnic nerves can hardly be prevented unless the proximal stump is implanted into a peripheral nerve. This was carried out on diabetic children on whom section of the splanchnic nerve had been per-

9. de Takáts, G., and Cuthbert, F. P.: Effect of Suprarenal Denervation and Splanchnic Section on the Sugar Tolerance of Dogs, Arch. Surg. **30**:151 (Jan.) 1935.

formed.[10] Simple section of the trunk of the thoracic sympathetic chain, as practiced by Royle,[11] is likely to be followed by regeneration, although no histologic proof in man has ever been presented. The complete removal of the ganglionated trunk with its postganglionic fibers can show evidence of regeneration only if (1) the operation did not remove all the excitor ganglions and if some postganglionic fibers escaped section or (2) if a preganglionic section of the trunk was carried out, after which the preganglionic fibers readily established connections with the intact ganglions and their postganglionic fibers. A third possibility is that the two-neuron theory of Langley—that the sympathetic nervous system consists of a massive syncytical network of fibers and ganglions—is incorrect. Not only are the ganglions present in the cord and in the sympathetic ganglions, but they are scattered in the periphery and are capable of regenerating fibers, of automatic function and of reflex activity. This theory has been advanced by Stöhr,[12] and should it be correct, regeneration of fibers and return of function could be explained even if complete, so-called preganglionic and postganglionic section had taken place. Restoration of peripheral resistance in completely sympathectomized animals has recently been reported by Wilson, Roome and Grimson,[13] from Phemister's department at the University of Chicago.

Should Stöhr's theory be correct and if regeneration and automatic activity of these peripheral ganglions and terminal network occurred after their severance from the cord, I still believe that permanent benefit is derived from sympathectomy. The lower centers, while active, will be uninhibited by higher nervous activity. Central and reflex stimuli do not reach them. They are stimulated by metabolic activities of the tissues and by thermal influences. So again one must come to the conclusion that the blood flow is more even and less inhibited than before operation. Only if the regeneration of the sympathetic fibers could reestablish normal connections with the cord would a preoperative state be reached.

However, until more evidence accumulates, the theory of Langley still stands, and there is ample histologic evidence to show that transection of preganglionic fibers leaves the terminal ganglion and post-

10. de Takáts, G.: Splanchnic Nerve Section in Juvenile Diabetes: II. Technic and Postoperative Management, Ann. Surg. **102**:22 (July) 1935.

11. Royle, N. D.: Sympathetic Trunk Section: A New Operation for Raynaud's Disease and Spastic Paralysis of the Upper Limb, M. J. Australia **2**:436 (Oct. 6) 1928.

12. Stöhr, P., Jr.: Bemerkungen zur Gefässinnervation, Zentralbl. f. Chir. **61**:2 (Jan. 6) 1934.

13. Wilson, H.; Roome, N. W., and Grimson, K.: Complete Sympathectomy: Observations on Certain Vascular Reactions During and After Complete Exclusion of the Sympathetic Nervous System of Dogs, Ann. Surg. **103**:498, 1936.

ganglionic fiber intact, whereas removal of the ganglion produces postganglionic degeneration but leaves the upper neuron intact.[14]

The regaining of vascular tonus has been interpreted recently as an increased sensitivity to hormones, such as epinephrine,[15] when the postganglionic fiber degenerates.[16] Therefore, following the advice of Smithwick, Freeman and White and Telford,[17] efforts have been made to restrict sympathectomy to preganglionic sections. My colleagues and I have had favorable experience with these operations. All lumbar sympathectomies are predominantly preganglionic sections, as the ganglions for the lower extremity are mostly in the lowest lumbar and upper sacral ganglions. In the upper extremity, however, the usual excision of the inferior cervical and first and second thoracic ganglions removes the excitor ganglions, and postganglionic degeneration occurs. To overcome this, Smithwick[18] has recently described preganglionic section for the upper extremity by sectioning the dorsal sympathetic chain below the third ganglion and removing the proximal inch (2.5 cm.) of the second and third intercostal nerves. More recently he has extended this operation so that the dissection of the intercostal nerves is carried into the intervertebral foramen and includes dividing the dural attachments and sectioning the anterior and posterior roots as well. In my clinic the Smithwick operation has been carried out only twice, whereas another approach from the front, as suggested by Telford, has been used sixteen times. Time will show the per-

14. Ransom, S. W.: The Anatomy of the Autonomic Nervous System with Special Reference to the Innervation of Skeletal Muscles and Blood Vessels, Ann. Int. Med. **6**:1013, 1933. Lawrentjew, B. I.: Weitere Untersuchungen über die Degeneration und Regeneration von Synapsen, Ztschr. f. mikr.-anat. Forsch. **35**:71, 1934. Lawrentjew, B. I., and Boroskaja, A. J.: Die Degeneration der postganglionären Fasern des autonomen Nervensystems und deren Endigungen, Ztschr. f. Zellforsch. u. mikr. Anat. **23**:761, 1936.

15. Freeman, N. E.; Smithwick, R. H., and White, J. C.: Reactions of the Blood Vessels of the Human Extremity, Sensitized by Sympathectomy to Adrenaline and to Adrenal Secretion Resulting from Insulin Hypoglycemia, Am. J. Physiol. **107**: 529, 1934.

16. As reported in a joint communication with Sanford Gifford (Cervical Sympathectomy in Retinitis Pigmentosa, Arch. Ophth. **14**:441 [Sept.] 1935), the difference of preganglionic and postganglionic sections on the effect of pupillary reactions to epinephrine can easily be demonstrated.

17. Smithwick, R. H.; Freeman, N. E., and White, J. C.: The Effect of Epinephrine on the Sympathectomized Human Extremity: An Additional Cause of Failure of Operations for Raynaud's Disease, Arch. Surg. **29**:759 (Nov.) 1934. White, J. C.: The Autonomic Nervous System, New York, The Macmillan Company, 1935. Telford, E. D.: The Technique of Sympathectomy, Brit. J. Surg. **23**: 448, 1935.

18. Smithwick, R. H.: Modified Dorsal Sympathectomy for Vascular Spasm (Raynaud's Disease) of the Upper Extremity, Ann. Surg. **104**:339, 1936.

centage of failures or recurrences after this type of preganglionic section; at present it is possible only to report the marked difference in the upper extremities of the four patients, each of whom had postganglionic section on one side and preganglionic section on the other side.

3. VASCULAR DISEASES FOR WHICH SYMPATHECTOMY IS PERFORMED NOT BEING DISEASES OF THE VASOMOTOR SYSTEM

While occasional authors[19] report inflammatory or degenerative changes in the ganglions removed by sympathectomy for Buerger's disease and for Raynaud's disease, the consensus is that the removed ganglions do not show any pathologic changes.[20] Our material has been examined for some time by Dr. Hassin, who has not found any histologic evidence of pathologic processes in the excised ganglions or trunks. Obviously, sympathectomy operates not by removal of diseased tissue but by alteration of function. As pointed out before, in Raynaud's disease the operation inhibits the fluctuations of vasomotor tonus, which may be enough to elicit a spasm in a sensitized or abnormally narrow artery. In Buerger's disease it puts the inflamed vessel at rest and interrupts a spinal reflex originating in segmental thrombi. It does the same in the reflex dystrophies, in acute osseous atrophy, causalgia or stump neuroma. In poliomyelitis with vasospasm the operation may interrupt an efferent vasoconstrictor impulse originating in irritative phenomena of the lateral horn or anterior roots. Rarely, however, one may encounter vasoconstrictor phenomena in organic lesions of the sympathetic nervous system, as have been described by Peet and Kahn.[21]

4. SLIGHT OR NEGLIGIBLE CLINICAL BENEFIT OF SYMPATHECTOMY

The argument that the clinical benefit of sympathectomy is often slight or negligible calls for an analysis of the causes of failure following sympathectomy. Mistaken diagnosis, mistaken indications, improper stages of the vascular disease, faulty technic, improper after-treatment and a poor follow-up are important factors in the obtaining of poor results. Summarily expressed, the surgeon who performs sympathectomies must be thoroughly familiar with peripheral vascular disease

19. Kuntz, A.: Sympathetic Ganglions Removed Surgically: A Histopathologic Study, Arch. Surg. **28**:908 (May) 1934. Sunder-Plassmann, P.: Untersuchungsergebnisse zur Grenzstrangchirurgie, Arch. f. klin. Chir. **183**:653 (Oct 28) 1935.

20. Craig, W. M., and Kernohan, J. W.: The Surgical Removal and Histologic Study of Sympathetic Ganglia in Raynaud's Disease, Thrombo-Angiitis Obliterans, Chronic Infectious Arthritis, and Scleroderma, Surg., Gynec. & Obst. **56**:767, 1933.

21. Peet, M. M., and Kahn, E. A.: Vasomotor Phenomena Allied to Raynaud's Syndrome, Arch. Neurol. & Psychiat. **35**:79 (Jan.) 1936.

and its remissions and exacerbations, as well as its spontaneous course, and should use, either alone or in collaboration with physicians well versed in peripheral vascular disease, all the medicinal aids and physical therapy available at present. This principle applies to the surgical treatment of the central nervous system, of the endocrine glands and of the gastro-intestinal tract. There is no reason for a surgeon who can approach a sympathetic chain and remove it to be successful when his contact with peripheral circulatory disease is meager.

COMMENT

It is worth emphasizing, then, that surgical treatment of the sympathetic nervous system in cases of peripheral vascular disease is successful when the patients are carefully selected. It does not cure the disease, as does the removal of a diseased appendix or gallbladder; it

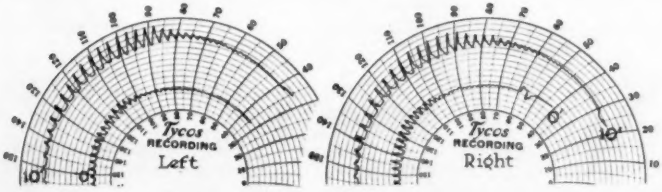

Fig. 4.—The sodium nitrite test. In A. M., a 31 year old woman suffering from Raynaud's disease of all four extremities, oscillometric curves for the ankles revealed a marked capacity for vasodilatation. The tests were run before and ten minutes after the intravenous administration of a freshly prepared solution of sodium nitrite. One cubic centimeter of 4 per cent solution is now being used routinely in the clinic. Note that ten minutes after the intravenous administration of sodium nitrite the spikes, representing the pulse beats, have increased in height; there is also a shift of these spikes toward the right. The difference is marked between 100 and 90 mm. of mercury before and after the administration of sodium nitrite.

only modifies perversions of functions the persistence of which is followed by a greater or lesser degree of organic damage. To test the capacity for dilatation of the vascular bed, a sodium nitrite test has been worked out, the details of which are being published elsewhere (fig. 4). This test enables one to eliminate patients who will not benefit from sympathectomy because of the extent of organic damage.

In analyzing the results of sympathectomy for Raynaud's disease (table 3) the following causes of failure have been recognized: (1) a *too advanced stage of disease* (stage 3), characterized by sclerosis of connective tissue, stiffness of the joints, sclerodactylia, ulcerations and inability to open the vascular bed with heat or sodium nitrite (the second and eighth patients belong to this group); (2) *incomplete denervation,* recognizable by residual sweating, usually over the ulnar area in the upper and the femoral-saphenous area in the lower

extremity (this was observed in the second patient of this series), and (3) *postoperative sensitization* due to postganglionic degeneration. The vessels in these areas are increasingly sensitive to epinephrine and solution of posterior pituitary. Since White's important emphasis on this cause of failure, sympathectomy on the upper extremities has always been performed so as to avoid postganglionic degeneration.

In studying the results of sympathectomy in Buerger's disease (table 4), the cause of failure can be found in trying to extend the use of sympathectomy to patients in whom the organic damage is too extensive. After my only fatal sympathectomy, due to coronary thrombosis, electrocardiographic records have been made for every patient with Buerger's disease. This patient (case 1) had extensive vascular damage of the coronary vessels and in the peripheral vessels,

TABLE 3.—*Results of Sympathectomy in Raynaud's Disease (Sixteen Sympathectomies on Six Patients)* *

Case No.	Name	Duration, Years	Stage of Disease	Operation		Result		Comment
1	Wanda F.	3	2	Preganglionic Postganglionic	1 1	Fair Failure	1 1	
2	Nettie S.	8	3	Postganglionic	2	Failure	2	Residual sweating
3	Adeline M.	6	2	Preganglionic Postganglionic Lumbar	1 1 2	Excellent Failure	3 1	Brachial neuritis, 6 wk.
4	Augusta J.	1	2	Preganglionic Postganglionic	1 1	Excellent Fair	1 1	
5	Phyllis Z.	10	2	Preganglionic Postganglionic	1 1	Excellent Fair	1 1	Brachial neuritis, 4 mo.
6	Kate S.	8	3	Postganglionic Lumbar	2 2	Fair Excellent	2 2	

* The patients in this series have been followed through at least one winter (three of them through two winters). By fair result is meant definite improvement, with fewer or shorter attacks, but not complete relief.

with superimposed arteriosclerosis. With the exception of this patient, all the patients were less than 40 years old and showed sufficient vasodilatation to heat or sodium nitrite to justify sympathectomy. The most marked effect was obtained on coldness and numbness, then on rest pain and ulceration; intermittent claudication, which in our experience is often improved by intermittent venous hyperemia,[22] is hardly influenced by sympathectomy. Sympathectomy was performed on the upper extremity to heal ulceration of the fingers or to prevent pulseless cold hands from becoming gangrenous. Collateral circulation here is so much more extensive that the operation can be performed in the presence of much more organic damage on the upper than on the lower extremity.

22. de Takáts, G.; Hick, F. K., and Coulter, John S.: Intermittent Venous Hyperemia, in Treatment of Peripheral Vascular Disease, J. A. M. A. **108**:1951 (June 5) 1937.

The results for the seven patients with causalgia, traumatic osteoporosis or poliomyelitis with vessel spasm are uniformly satisfactory, mainly because organic vascular damage is slight and occurs only late in the course of the disease (table 5). One cannot subscribe to the

TABLE 4.—*Results of Sympathectomy in Buerger's Disease (Twenty-Two Sympathectomies on Ten Patients)*

Case No.	Name	Age	Operation	Effect on*				Comment
				Coldness and Numbness	Claudication	Rest Pain	Ulceration	
1	John H.	48	Lumbar.....2	0	0	0	..	Died on fifth day of coronary occlusion
2	Maurice V. T.	31	Preganglionic..2	+++	+	+++	..	Excellent
3	Sam S.	36	Lumbar.....2	+++	0	++	+++	Excellent
4	Sol L.	39	Lumbar.....2	+++†	+	+++	..	Excellent
5	F. N.	38	Preganglionic..2 Lumbar.....2	+++ —	++ 0	.. +	..	Fair on lower, excellent on upper extremities
6	A. T.	35	Preganglionic 1 Lumbar.....2	+++ 0	0 0	++ 0	..	Bilateral amputation
7	A. R.	36	Preganglionic 1	+++	+	+++	..	Excellent
8	George G.	30	Preganglionic..1 Lumbar.....1	+++ +++	.. +	+++ +++	.. ..	Excellent
9	J. A.	31	Lumbar.....2	+++	—	+++	..	Fair
10	J. D.	28	Lumbar.....2	+++	++	—	..	Excellent

* +++ indicates complete relief; ++, greatly improved; +, better; 0, no effect, and —, absent before operation. Claudication was gaged according to ability to walk at a rate of ten paces in five seconds until cramping occurred.
† Crushing of the peripheral nerve produced this result.

TABLE 5.—*Results of Sympathectomy for Peripheral Circulatory Disturbances, 1928 to 1935*

Diagnosis	Number of Patients	Number of Operations	Number of Operations Followed by			
			Success	Improvement	Failure	Death
Raynaud's disease	6	16	7	5	4	..
Buerger's disease	10	22	15	4	2	1
Poliomyelitis	3	3	3	..	..	..
Reflex dystrophy	5	5	5	..	..	..
Total	24	46	30	9	6	1

argument, then, that clinical results of sympathectomy are poor. When they are, a mistake has been made somewhere. The factors involved have been enumerated.

SUMMARY

The arguments against sympathectomy have been discussed, and it has been shown that operation on the sympathetic nervous system is worthy of consideration for selected patients with peripheral vascular disease.

ORIGIN OF NEUTROPHILS IN PERNICIOUS ANEMIA (COOKE'S MACROPOLYCYTES)

BIOPSIES OF BONE MARROW

OLIVER P. JONES, PH.D.
MINNEAPOLIS

It has been aptly mentioned by Heck and Watkins [1] that there is little in the American medical literature concerning the value of neutrophils in pernicious anemia as an aid to diagnosis. There is practically nothing in the American literature dealing with the origin of these cells. Cooke,[2] after studying cells in the peripheral blood for many years, finally advanced three hypotheses to explain the source of large hypersegmented hyperpolymorphic neutrophils in pernicious anemia, which he called macropolycytes I, II, and III. These are the same cells which have been called pernicious anemia neutrophils and have been accurately described by Downey.[3] As will be seen later, the various types of macropolycytes described by Cooke are in reality morphologic variations of cells belonging to the same series of pathologic neutrophils.

The origin of these atypical cells was contemplated in the following hypotheses formulated by Cooke:[2] First, there is some biochemical change in the plasma which causes the cell to age prematurely and become hypersegmented. Second, there may be something amiss with the mechanism which normally eliminates neutrophils from the circulation, thereby producing abnormally matured neutrophils. Third, the polymorphonuclears may be inherently abnormal, owing to a defect in the parent cells, or there may be some single defect in the cellular environment which is responsible for all the changes manifested in the macropolycytes, since after the administration of liver these cells and

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1. Heck, F. J., and Watkins, C. H.: The Neutrophil in Pernicious Anemia, Am. J. Clin. Path. **3**:263 (July) 1933.

2. Cooke, W. E.: The Macropolycyte, J. Lab. & Clin. Med. **19**:453 (Feb.) 1934.

3. Downey, Hal: Diseases of the Blood, in Bell, E. T.: Textbook of Pathology, Philadelphia, Lea & Febiger, 1934.

the abnormal cells of the hemoglobiniferous series disappear. Furthermore, Cooke and Ponder [4] have stated: "There does not appear any doubt that these cells commence life in the blood stream as simple nucleated types." Accordingly these cells would then become hypersegmented as they matured. It is for this reason that macropolycytes ("pernicious anemia neutrophils") have been likened to megakaryocytes of the marrow, because the nucleus is gnarled and the coarse granules are somewhat azurophilic.[5] Cooke [2] stated later that they do not resemble any embryonic or adult blood cell and are not exact replicas of the megakaryocyte.

Cooke and Ponder [4] have assumed that these cells arise from hemocytoblasts, the potentialities of which have been altered by environmental changes. Normally the hemocytoblast may develop into either a granulocyte or a megakaryocyte, but under altered conditions of environment it attempts to differentiate simultaneously along these two lines. Hence, if the bias is megakaryocytic, then a megakaryocytic type of macropolycyte develops. Although Cooke [2] has stated that he considers these possible modes of origin for macropolycytes, he has cast aspersion on a myeloid origin of the cells, claiming that they might even originate in mesenchymal descendants in the liver or in hemolymph nodes that have undergone abnormal metaplasia. On the other hand, Piney [6] found that there is morphologic evidence of defective marrow function, in that hyaline leukocytes (monocytes) are always reduced and there is always a varying number of neutrophils of large size with hypersegmented nuclei.

The first investigators seriously to consider the problem of establishing the origin of these abnormal neutrophils in pernicious anemia were Tempka and Braun,[7] who studied biopsy specimens of the bone marrow of patients with pernicious anemia. Their findings followed closely those anticipated in Cooke's third hypothesis. These workers observed alterations in the myeloblasts, metamyeloblasts (leukoblasts?), promyelocytes, myelocytes and metamyelocytes. The most profound alteration was noted, however, in cells which they interpreted to be "grössere pathologische stabkernige Neutrocyten." The tortuous

4. Cooke, W. E., and Ponder, E.: The Polynuclear Count, London, Charles Griffen & Co., Ltd., 1927.

5. Cooke, W. E.: The Macropolycyte, Brit. M. J. **1**:12 (Jan. 1) 1927; Further Observations on the Macropolycyte, ibid. **1**:800 (May 4) 1929.

6. Piney, A.: Pernicious Anaemia: Some Morphological and Etiological Considerations, Brit. M. J. **1**:271 (Feb. 16) 1924.

7. Tempka, T., and Braun, B.: Das morphologische Verhalten des Sternumpunktates in verschiedenen Stadien der perniziösen Anämie und seine Wandlungen unter dem Einflusse der Therapie, Folia haemat. **48**:355, 1932.

nuclei in these cells occupy about two thirds of the cytoplasm. The basichromatin is coarse in some places, while in others it may be loosened so that oxychromatic spaces are distinct. Frequently there are vacuoles in the nucleus, and one of the more constant characteristics is the appearance of large cytoplasmic vacuoles. Here and there groups of clear spaces may be seen in the cytoplasm, with transitions to fully developed vacuoles. Patchy, confluent areas of basophilia may appear in light oxyphilic cytoplasm. The granulation is copious, unevenly large and irregularly distributed. In the same cell, adjacent to the neutrophilic granulation, there may be some azurophilic progranulation. These pathologically altered stab forms appear to arise directly from promyelocytes without passing through the intermediate myelocytic and metamyelocytic developmental stages. The evidence for this is that some promyelocytes show pronounced indentations and contractures, and all transitions to the stab form exist. Also, the nuclear structure in the stab form is practically identical with that of the promyelocyte. Tempka and Braun have recognized three types of developing neutrophils in the marrow of patients with pernicious anemia, i. e., large, medium and small elements. These cells are separated from one another not only by their size but by their intrinsic structure, which is most essential for the identification of pathologic forms.

It must be emphasized that the marrow is not entirely composed of these pathologic elements, for normal granulocytic development is also taking place to a lesser degree. From these observations Tempka and Braun were led to conclude that there is a regenerative-degenerative change in the neutrophilic series. Indications of degenerative alterations include structural alterations of the basichromatin, an increased number of damaged cells and the presence of vacuoles. Indications of pathologic regeneration include: basophilia of the cytoplasm, azurophilic progranulation, disproportionate developmental stages between the nucleus and the cytoplasm, doubled nuclei and an abnormal cell size.

Other investigators [8] have more or less confirmed the observations made by Tempka and Braun [7] on biopsy specimens of bone marrow of patients with pernicious anemia during a relapse. Segerdahl [8a] has

8. (*a*) Segerdahl, Elsa: Ueber Sternalpunktionen, Uppsala, Appelbergs Boktryckeriaktiebolag, 1935. (*b*) Barta, I.: Die Bedeutung der Sternalpunktion bei Anämien und über die Beeinflussung des Knockenmarkes durch Leberbehandlung, Deutsches Arch. f. klin. Med. **171**:565, 1931. (*c*) Nordenson, N. G.: Studies on Bone Marrow from Sternal Puncture, Stockholm, Börtzells, Esselte, 1935. (*d*) Rohr, K.: Die diagnostische Bedeutung der Sternalpunktion, Helvet. med. acta **1**:713, 1935; Ueber Bedeutung und Ergebnisse der Sternalpunktion, Praxis **24**:326 (June 26) 1935. (*e*) Henning, N.: Ueber die bisherigen Ergebnisse der intravitalen Knochenmarkuntersuchungen, Med. Klin. **32**:542 (April 17) 1936. (*f*) Young, R. H., and Osgood, E. E.: Sternal Marrow Aspirated During Life: Cytology in Health and in Disease, Arch. Int. Med. **55**:186 (Feb.) 1935.

reported that even the nuclei of myeloblasts commence to be polymorphic and may be in the developmental stage of a myelocyte or metamyelocyte, some of which show a tortuous and fantastic shape. Eventually these forms transform into the hypersegmented leukocytes which are often much enlarged. Therefore, hypersegmentation is not a true expression of the age of a cell. Barta [8b] likewise claimed that hypersegmentation is not a criterion of age but rather an expression of altered function of the bone marrow. Nordenson [8c] observed that maturation process in promyelocytes and myelocytes is disturbed, causing these cells to become much larger than is normally in keeping with their age. Unlike Segerdahl, Nordenson did not find marked changes in the myeloblast.

Similarly, Rohr [8d] has reported that the nuclei have a tendency to become hypersegmented and polymorphic during the myelocyte and metamyelocyte stages. Henning [8e] has found the abnormalities of the neutrophilic series to be the most striking alteration of bone marrow caused by pernicious anemia. Young and Osgood [8f] reported that "a few multilobulated neutrophils and giant staff cells are present" but made no mention of the regenerative-degenerative changes reported by Tempka and Braun.[7] In one article Dameshek [9a] did not mention the abnormal developmental stages of the neutrophil in marrow during pernicious anemia. Later, Dameshek and Valentine [9b] stated that "the huge bizarre forms of metamyelocytes suggest monstrosities in cellular development." They stated as their belief that these cells are responsible for the hypersegmented neutrophils of the peripheral blood. Others [10] have also found precocious abnormal polymorphism and segmentation of neutrophils in the marrow, which they have claimed explains the cause for the appearance of "pernicious anemia neutrophils" in the peripheral blood. Many other investigators [11] have studied

9. (*a*) Dameshek, W.: Biopsy of the Sternal Bone Marrow, Am. J. M. Sc. **190**:617, 1935. (*b*) Dameshek, W., and Valentine, E. H.: The Sternal Marrow in Pernicious Anemia: Correlation of the Observations at Biopsy with the Blood Picture and the Effects of Specific Treatment in Megaloblastic ("Liver-Deficient") Hyperplasia, Arch. Path. **23**:159 (Feb.) 1937.

10. Jaffé, R. H.: The Bone Marrow, J. A. M. A. **107**:124 (July 11) 1936. Jagić, N., and Klima, R.: Zur Klinik und Differentialdiagnose der Anämien mit besonderer Berücksichtigung der Knochenmarkspunktion, Wien. klin. Wchnschr. **48**:282 (March 1) 1935. Markoff, N.: Die Beurteilung des Knochenmarks durch Sternalpunktion, Deutsches Arch. f. klin. Med. **179**:113, 1936. Yamamoto, T.: Die feinere Histologie des Knochenmarkes als Ursache der Verschiebung des neutrophilen Blutbildes: Vergleichende experimentelle pathologisch-anatomische und klinische Untersuchungen, Virchows Arch. f. path. Anat. **258**:62, 1925.

11. (*a*) Arinkin, M. I.: Die intravitale Untersuchungsmethodik des Knochenmarks, Folia haemat. **38**:233, 1929. (*b*) Doan, C.: The Type of Phagocytic Cell and Its Relative Proportions in Human Bone Marrow and Spleen, as Identified by the Supravital Technique, J. Exper. Med. **43**:289, 1926. (*c*) Doan, C., and

(Footnote continued on next page)

the bone marrow of patients with pernicious anemia during a relapse and either have failed to observe these profound alterations of the neutrophilic series or else have neglected to mention them.

MATERIAL

The present investigation was carried out on fifteen biopsy specimens of bone marrow from patients with pernicious anemia during a relapse.[12] Eight were prepared by smearing freshly aspirated sternal marrow, and seven were dry imprint (*Abklatsch*) preparations. All preparations were stained with the May-Grünwald-Giemsa combination stain of Pappenheim. The best morphologic detail of the marrow cells was elicited by the dry imprint method; consequently these preparations were studied more intensively than films of aspirated marrow. Since this paper is concerned chiefly with the origin of pathologic cells encountered in the peripheral blood, it is obvious that the method of choice would have to be the dry imprint or dry smear method. These are the only methods which bring out the finer structural details, especially of the nucleus, which is so important for the proper identification of the immature "lymphoid" cells that have not developed specific cytoplasmic characters

OBSERVATIONS

My previous studies[13] have revealed that the large neutrophils (macropolycytes) in pernicious anemia have an entirely different life history from that of the neutrophils in normal bone marrow. One of the most striking features is the marked anisocytosis and macrocytosis of the leukopoietic elements. Leukoblasts and promyelocytes

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Zerfas, L.: The Rhythmic Range of the White Blood Cells in Human, Pathological Leucopenic and Leucocytic States, with a Study of Thirty-Two Human Bone Marrows, ibid. **46**:511, 1927. (*d*) Escudero, P., and Varela, M. E.: La biopsia del midollo osseo nelle sue applicazioni in ematologia, Haematologica, II. Recen. **3**:65, 1932. (*e*) Holmes, W. F., and Broun, G. O.: Clinical Study of Bone Marrow by the Method of Sternal Puncture, Proc. Soc. Exper. Biol. & Med. **30**:1306, 1933. (*f*) Isaacs, R.: The Bone Marrow in Anemia, Am. J. M. Sc. **193**:181 (Feb.) 1937. (*g*) Peabody, F. W.: The Pathology of the Bone Marrow in Pernicious Anemia, Am. J. Path. **3**:179 (May) 1927. (*h*) Roversi, A. S., and Tanturri, E.: La puntura dello sterno nella practica medica, Haematologica **16**: 1, 1935. (*i*) Weiner, W., and Kaznelson, P.: Ueber die zellige Zusammensetzung des Knochenmarkes nach Erfahrungen mittels der Sternalpunktion nach Seyfarth, Folia haemat. **32**:233, 1926. (*j*) Heilbrun, N.: The State of the Sternal Bone Marrow in a Case of Macrocytic (Pernicious) Anemia of Pregnancy, J. A. M. A. **107**:27 (July 4) 1936.

12. This material was made available through the cooperation received from Dr. Cecil J. Watson and other members of the staff of the department of medicine, the University of Minnesota Medical School.

13. Jones, O. P.: (*a*) Cytological Studies of Biopsied Pernicious Anemia Bone Marrow During Relapse, Proc. Soc. Exper. Biol. & Med. **34**:694, 1936; (*b*) Cytology of Pathologic Marrow Cells, with Special Reference to Bone Marrow Biopsies, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., to be published.

may be two or three times as large as corresponding normal cells. Another outstanding alteration is found in the complex and bizarre arrangement of the nuclei in various developing neutrophils. On the whole, my observations agree well with those of Tempka and Braun,[7] but, as will be seen later, the interpretation is different.

Pathologic alterations were found in the myeloblast, leukoblast, promyelocyte and myelocyte stages of development. In some instances the alterations were such that it was extremely difficult to decide to which category a given cell belonged. The earliest change observed in the myeloblast was a slight tendency toward polymorphism. Tempka and Braun [7] observed an absence of nucleoli in many myeloblasts and said that they considered this to be due to a pathologic alteration. However, I do not attach much significance to this fact, since it has been shown that the presence of nucleoli is variable in myeloblasts.[14] Some myeloblasts were extremely basophilic, almost as basophilic as promegaloblasts; but here again one is dealing with another variable characteristic. Tempka and Braun [7] have reported a loosening and thickening of the chromatin net in some myeloblasts. This was never observed in my material. Cytoplasmic vacuoles were present in some myeloblasts.

A more pronounced nuclear polymorphism is generally found in the leukoblast stage, which possibly corresponds to the metamyeloblast of Tempka and Braun.[7] This type of cell, with peculiar protuberances and invaginations of the nucleus, is shown in figure *2a*. There may be vacuoles in the cytoplasm and some azurophilic granulation. However, many of the leukoblasts of the present series were without azurophilic granulation.

Some large promyelocytes were found with normally shaped nuclei, while in a few cells the nucleus was like a giant band (stab) form (fig. *2b*). Others had a hyperpolymorphic nucleus. Cytoplasmic vacuoles were present, as well as perforations in the nuclear material. Some promyelocytes had coarse azurophilic granulation, while others had only the slightly metachromatic granules of beginning specific neutrophilic granulation. No direct relationship was observed to exist between azurophilic and specific granulations, as Downey [14] has already shown. I [15] have also shown that the presence of azurophilic granules does not necessarily indicate differentiation toward the granulocytic series. These atypical promyelocytes possessed a cytoplasmic basophilia of varying

14. Downey, Hal: (*a*) The Myeloblast: Its Occurrence Under Normal and Pathological Conditions, and Its Relations to Lymphocytes and Other Blood Cells, Folia haemat. **34**:65 and 145, 1927; (*b*) The Myeloblast, in Handbook of Hematology, New York, Paul B. Hoeber, Inc., to be published.

15. Jones, O. P.: Atypical Azurophilic Granulation in Megaloblasts, Folia haemat. **55**:195, 1936.

intensity. Cells were considered to be in this stage of development as long as there was a reasonable amount of basophilia remaining in the cytoplasm. If the cytoplasm contained a full quota of specific granules, the cell was considered to be in the myelocyte stage. Since there is such a great disparity between the maturation of the nucleus and that of the cytoplasm, nuclear criteria cannot always be relied on in determining the exact level of development.

In the myelocyte stage the atypical neutrophils have a cytoplasm that is completely filled with granules that are more acidophilic and larger than normal. Cytoplasmic vacuoles may be present, but as a

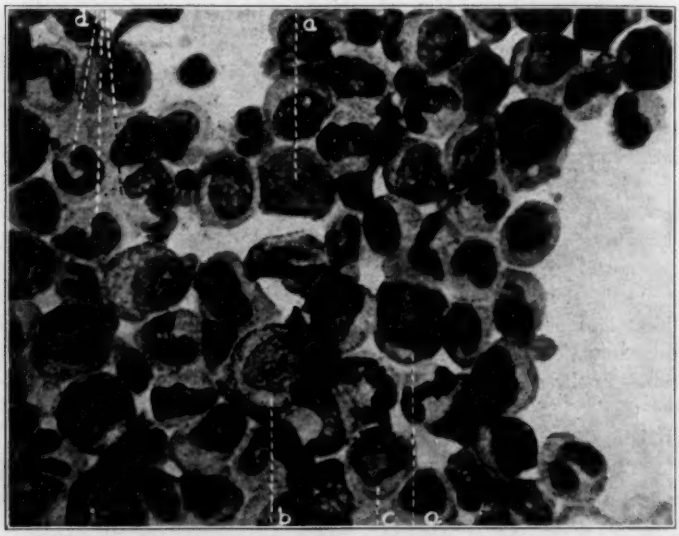

Fig. 1.—Imprint of fresh rib marrow obtained from a patient with chronic empyema. This particular marrow was selected rather than normal marrow because, even though there is a marked increase in metamyelocytes and band forms, they are never as large or polymorphic as the cells shown in figures 2 and 3. *a* indicates a pronormoblast (pro-erythroblast). Cells similar to this are undoubtedly the ones Doan and Zerfas [11c] misinterpreted for "megaloblasts." *b* indicates a normal neutrophilic promyelocyte. *c* indicates a normal neutrophilic myelocyte; *d*, normal neutrophilic metamyelocytes. Compare *b*, *c* and *d* with the pathologic cells shown in figures 2 and 3. May-Grünwald-Giemsa stain. The magnification is the same for figures 1 to 3.

rule these tend to disappear during this stage of development. Therefore, the presence of vacuoles in earlier stages of development is indicative of an abnormal maturation rather than a sign of degeneration. The nuclear configuration is complex and bizarre (fig. 2 *c*). Generally the

arrangement of chromatin is less compact than that of corresponding stages in the normal neutrophil. Some of these atypical myelocytes may have one or more perforations in the nuclear material, in addition to a hyperpolymorphic configuration. These holes in the nucleus commence as areas of rarefaction and ultimately become a single, definitely circumscribed hole (fig. 3 *a*). In cross-section the perforations appear initially as invaginations in the nuclear mass. The actual perforation occurs after opposite invaginating nuclear membranes come in contact. Some myelocytes (fig. 3 *a*) have a single large circular hole, which gives them the appearance of a torus (doughnut). Other pathologic neutro-

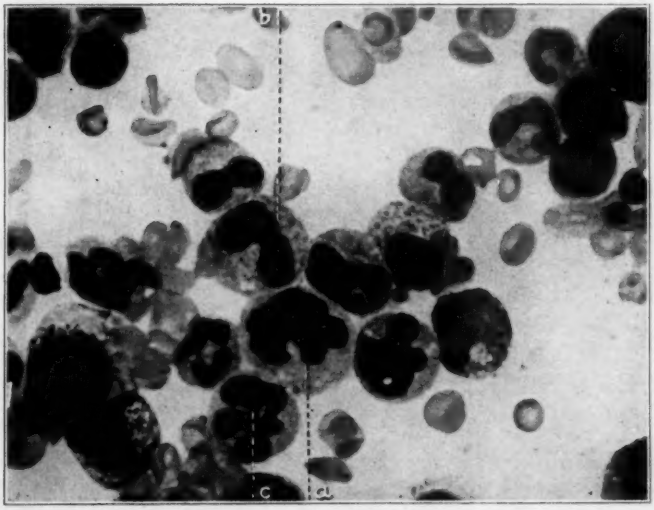

Fig. 2.—Imprint of marrow obtained for biopsy from a patient with pernicious anemia during a relapse. *a* indicates a hyperpolymorphic leukoblast with several areas of rarefaction in the cytoplasm; *b*, an atypical promyelocyte of the neutrophil series in pernicious anemia. The cytoplasm is faintly basophilic and contains two vacuoles and early neutrophilic granulation. The nucleus is like a giant band form. *c* indicates an older atypical myelocyte. Note the peculiar nuclear protuberances. May-Grünwald-Giemsa stain.

philic myelocytes are found to have three or more holes in the nucleus, separated from one another by a strand of chromatin which varies in thickness. These nuclear perforations may develop to such an extent that they are finally bounded on two sides by a thin strand of chromatin. Not all the atypical neutrophilic myelocytes undergo a nuclear perforation during maturation. Instead, some develop elongated, band-shaped nuclei (fig. 3 *b*). These cells have been described by Tempka

and Braun [7] as *grössere pathologische stabkernige Neutrocyten.* In these forms the nucleus may become so twisted and convoluted that there is overlapping. These alterations have been interpreted by Tempka and Braun [7] as indicating degenerative manifestations. Contrary to this, I believe that these nuclear changes express the manner in which the pathologic neutrophilic myelocyte ultimately attains the morphology of "macropolycytes II and III" described by Cooke [2] or the "pernicious anemia neutrophil" of the peripheral blood described by Downey.[3]

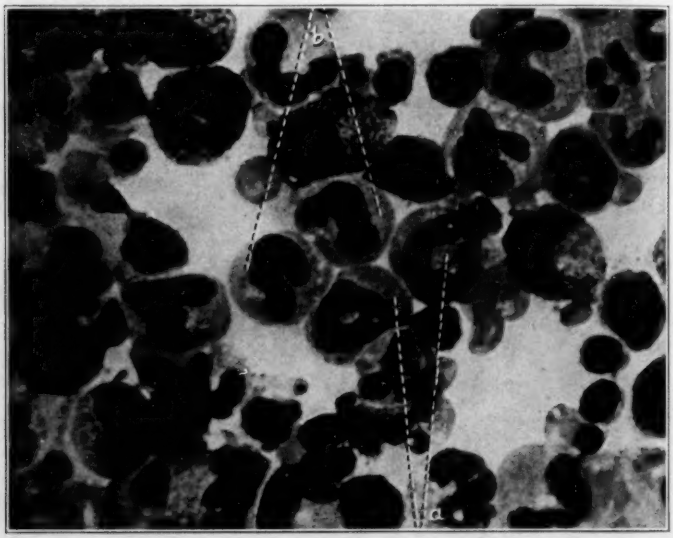

Fig. 3.—Imprint of marrow obtained for biopsy from a patient with pernicious anemia during a relapse. *a* indicates atypical neutrophilic myelocytes showing the peculiar perforations of nuclear material; *b*, atypical neutrophilic myelocytes with large band-form nuclei. Note the other hyperpolymorphic neutrophils in the field and compare these with normal-sized metamyelocytes and band forms in figure 1. May-Grünwald-Giemsa stain.

From the foregoing description it can be seen that I was able to find abnormalities in every stage of neutrophilic development. This is contrary to the observations made by Dameshek and Valentine,[9b] who found maldevelopment occurring only in the neutrophilic metamyelocytes and occasionally in myelocytes. However, their figures do not support this contention. Their cells *a* and *b* in figure 4 appear to have a basophilic cytoplasm with few granules. My interpretation is that

these cells represent promyelocytes (as determined by the cytoplasm) which have undergone a precocious nuclear polymorphism.

COMMENT

Since it has been shown that the neutrophils seen in pernicious anemia are important as an aid in the diagnosis of macrocytic anemias,[16] it seems only natural that considerable attention should be directed toward the determination of the origin of these neutrophils. My observations and those which were mentioned in the review of the literature furnish ample evidence to indicate that the hyperpolymorphic and hypersegmented neutrophils in the peripheral blood of patients with pernicious anemia do not enter the blood as simple nucleated forms. Furthermore, studies of the bone marrow of patients with pernicious anemia have revealed that these neutrophils have a life history (ontogeny) which is abnormal throughout and different from that found in normal human marrow. While the marrow undoubtedly produces the majority of these pathologic neutrophils, it cannot be denied that these neutrophils may also be produced to a limited extent in other organs as a result of myeloid metaplasia.

It is significant that the neutrophils seen in pernicious anemia are not merely functional alterations of normal neutrophils, such as the "toxic" and pathologic neutrophils encountered in the peripheral blood in certain septic conditions. I believe it is justifiable to assume that there is a true pathologic regeneration of neutrophils in the marrow in pernicious anemia during a relapse which results in the production of a pathologic neutrophilic series. The morphologic evidence for this assumption is as follows: the precocious nuclear polymorphism, the nuclear pattern which is different from normal, cells two to three times larger than normal, granules larger and more acidophilic than normal, the cytoplasmic vacuolation and the nuclear perforation. (This whole process reminds one of the granulocytic development which sometimes proceeds from Rieder cells in the leukemias.) There are no signs of "toxic degeneration," such as pyknotic nuclei and "toxic" granulation, in these pathologic neutrophils.

There is considerable variation in the nuclear configuration of neutrophils which have been produced by this pathologic regeneration. This is due to the fact that precocious nuclear polymorphism may commence in the leukoblast, the promyelocyte or the myelocyte stage. Therefore, the more mature forms of neutrophilic development have nuclei exhibit-

16. (*a*) Heck and Watkins.[1] Downey.[3] (*b*) Fallon, M.: Classification of the Anemias, Blood Pictures of the Anemias and Anemias in Infancy and Childhood, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., to be published.

ing various degrees of complexity. Then, too, all the pathologic neutrophils do not pass through a stage of development in which there are perforations in the nuclear material. The "macropolycytes I, II and III" described by Cooke are in reality morphologic variants of the same pathologic neutrophilic series. Hence, there is no necessity for subdividing the neutrophils of pernicious anemia into three different types, but it is essential to recognize the many morphologic forms they may assume. Since these forms have been adequately described by Heck and Watkins,[1] Downey [3] and Fallon [16b] elsewhere, repetition is not necessary here.

If it is concluded that the relative age of neutrophils can be determined by the degree of nuclear segmentation, then one must assume that the neutrophil of pernicious anemia has actually undergone precocious senility in the marrow. This condition may be the result of a faulty mechanism of delivery which causes the cells to remain in the marrow longer than normal. However, it seems more likely that hypersegmentation in these neutrophils is an indication of an alteration in the function of the bone marrow beginning in the earliest stages of neutrophilic development, rather than a criterion of age.[17] The evidence at hand indicates that the neutrophils of pernicious anemia have a hyperpolymorphic nucleus before they enter the blood stream, but it cannot be denied that these cells may continue to become even more polymorphic after they have once entered the blood stream. It is on the basis of this extreme nuclear polymorphism that the neutrophils (macropolycytes) of pernicious anemia have been likened to megakaryocytes.[18] Even at best, this similarity is superficial, for at no time during the course of their development do these pathologic neutrophils have a chromatin pattern simulating that of a megakaryocyte.

It is paradoxic that a lack of the principle potent against pernicious anemia should cause the production of giant neutrophilic promyelocytes and myelocytes as well as the much enlarged forms of the megaloblastic series. Some investigators have thought that the oligocythemia in pernicious anemia is caused by a blocking of the marrow with megaloblasts. In the same manner the leukopenia of pernicious anemia might be explained as the result of the blocking of the bone marrow with giant neutrophils. Davidson and Gulland [19] have advanced certain ideas

17. N. von Jagić and R. Klima have recently stated that the cells are not over aged, as was formerly assumed, but as a result of the premature onset of segmentation they are too extensively segmented (Ueber die diagnostische Bedeutung der Knochenmarkpunktion, Wien. klin. Wchnschr. **50**:363 [March 19] 1937).

18. Cooke and Ponder.[4] Cooke.[5]

19. Davidson, L. S. P., and Gulland, G. L.: Pernicious Anaemia, London, Henry Kimpton, 1930.

concerning the nature of leukopenia in pernicious anemia which I believe are worthy of quoting. They have said:

> Considering the vast increase in the amount of active marrow in this disease, the number of marrow leucocytes must be greatly in excess of the normal. In view of this it is difficult to explain the constant leucopenia and the rarity of leucocytosis, even in the presence of severe septic complications, unless one assumes that the absence of the specific liver factor in some way interferes with the passage of leucocytes into the blood, or with the transformation and maturation of myelocytes into the polymorphonuclear forms. The latter seems the more likely, and we suggest that liver is responsible not only for the proper performance of the normoblastic function, but also for the ripening of the neutrophilic leucocytes.

Storti [20] has differed with Davidson and Gulland by claiming that there is a reduction in the total leukopoietic tissue at the expense of the more mature forms and that there is complete disappearance of hemocytoblasts (myeloblasts). He has interpreted this to indicate a tendency toward arrest of maturation. Vlados and Bondarenko [21] have also reported an arrest of leukopoietic activity during a relapse.

If there is an arrest of maturation in pernicious anemia, it certainly is not similar to the arrest which Fitz-Hugh and Krumbhaar [22] and Darling, Parker and Jackson [23] found in agranulocytosis. At present there is no suitable explanation for the leukopenia in pernicious anemia. One or all of the aforementioned factors may play a part in its production, or it may be due to what Naegeli [24] has called biologic torpor of the bone marrow.

Since the advent of liver therapy for pernicious anemia a great deal of attention has been directed toward the so-called inhibition of differentiation at the "megaloblast stage" during relapse. Also, in the field of experimental hematology attempts have been made to produce macrocytic anemia with a megoblastic bone marrow. So much consideration has been given to this one particular condition of the marrow that the exact status of other myeloid components has been neglected by the majority of American workers.

Although various investigators have suggested or assumed that there is an involvement of the entire marrow, rather than just the hemoglobiniferous cells, Tempka and Braun [7] were the first to make a

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20. Storti, E.: Studio in vivo del midollo osseo nell' anemia perniciosa, Haematologica **18**:1, 1937.

21. Vlados, C., and Bondarenko, E.: Étiologie et pathogénie de l' anémie de Biermer, Sang **8**:369, 1934.

22. Fitz-Hugh, T., and Krumbhaar, E. B.: Myeloid Cell Hyperplasia of the Bone Marrow in Agranulocytic Angina, Am. J. M. Sc. **183**:104, 1932.

23. Darling, R. C.; Parker, F., and Jackson, H.: The Pathological Changes in the Bone Marrow in Agranulocytosis, Am. J. Path. **12**:1 (Jan.) 1936.

24. Naegeli, O.: Ueber die Entstehung und Behandlung der Anämien, Wien. klin. Wchnschr. **48**:225 (Feb. 22) 1935.

qualitative study of other myeloid cells. They found that there is a panmyelopathy in pernicious anemia during a relapse. This consists of the appearance of numerous cells belonging to the pathologic hemoglobiniferous series, i. e., promegaloblasts and megaloblasts and megalocytes; numerous "grosse stabkernige Neutrozyten," with the variegated picture of degenerative-regenerative transformations, and severe impairment of the megakaryocytic system. They found that lymphocytes were also effected in the majority of cases. These were not only increased in number but in some instances showed nuclear pyknosis.

Tempka and Braun's concept of panmyelopathy of the marrow in pernicious anemia during a relapse has been recently confirmed by Dameshek and Valentine [9b] and myself.[13] However, the interpretation which I have finally given this panmyelopathy is different from that of Tempka and Braun. I agree that the lack of principle potent against pernicious anemia causes a proliferation of a pathologic red cell series, the megaloblasts. This series has its early stages of development as well as hemoglobin-bearing megaloblasts.[13b] The latter illustrates that there is not an inhibition of differentiation at the so-called "megaloblast stage," contrary to the general belief in this country. Cells of the normoblastic or definitive series are present, but their maturation is inhibited. (It is interesting to note that Storti [20] found the number of normoblastic cells to be equal to or even greater than the number in normal bone marrow.) I do not agree regarding the alterations in the neutrophils, which, according to my view, are not degenerative manifestations. The neutrophilic series is affected to the extent that there is developing in the marrow a pathologic series which gives rise to the abnormal neutrophils (macropolycytes) of the peripheral blood of patients with pernicious anemia. Also, the megakaryocytes are not as severely damaged or degenerated as Tempka and Braun have claimed, but they are pathologically altered so that they are not producing platelets.[13b] No doubt the lymphocytes may also be affected as reported.[25] Unfortunately I have not made any detailed studies of the lymphocytes as yet and therefore cannot confirm these observations.

At present I am unable to state whether the aforementioned pathologic neutrophilic series is limited solely to anemias due to deficiency of liver principle or whether the neutrophils are found in the marrow in other pathologic conditions also. Tempka and Braun [7] have claimed that these cells are not specific for pernicious anemia, since they found them in the marrow of patients with lymphogranuloma, carcinoma of the stomach and myelogenous leukemia. On the other hand, Nordenson [8c] claimed that the cytoplasmic and nuclear vacuolation of the

25. Tempka and Braun.[7] Dameshek and Valentine.[9b]

neutrophils is almost pathognomonic of pernicious anemia. Furthermore, Henning [8c] has reported the pathologic neutrophils to be the most striking alteration of the bone marrow in pernicious anemia.

It is obvious from these studies that a lack of the principle potent against pernicious anemia produces a profound effect on the entire bone marrow. They also show that there is definitely more at fault than a failure of red blood corpuscles to differentiate from the so-called megaloblast stage. Further study may reveal that a lack of the principle potent against pernicious anemia has it primary effect on the myeloblast (stem cell) or even the reticulo-endothelium.[26]

Dr. Hal Downey was a constant source of help and advice throughout the course of this investigation.

26. The Italian school of hematology (Ferrata, di Guglielmo, Villa, Introzzi and Storti) has maintained that there is a systemic disturbance of the connective tissue involving the "hemohistioblasts" in pernicious anemia. Recently Storti [20] reported that hemocytoblasts (myeloblasts) were absent from the marrow during relapse and offered this observation as further proof of the "histioid" or mesenchymal nature of pernicious anemia. However, we do not believe this condition has been proved, since Ringoen (Folia haemat. **33**:149, 1927) has shown that "hemohistioblasts" are artefacts and that these are the cells on which the Italians have formulated their theory. In our material there was no evidence that neutrophils were formed directly from the reticulo-endothelium without passing through the myeloblast stage.

THE HEART IN ACUTE NEPHRITIS

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The effect of acute glomerulonephritis on the heart has received little study in this country in recent years. Yet in 1879 Goodhart [1] pointed out the occurrence of heart failure in this disease and reported dilatation of the heart at necropsy, with fatty degeneration of the cardiac muscle in one case. Other authors confirmed the clinical observation and, notably Volhard and Fahr,[2] emphasized the frequency of dyspnea, orthopnea and pulmonary edema. Levy [3] cited the literature up to 1930 and described additional cases in which the presenting symptoms were those of heart failure. In agreement with the majority of previous writers on the subject, he ascribed the cardiac failure to strain placed on the heart by the sudden onset of hypertension in acute nephritis. Further study of the disease, however, suggested that there is also a widespread vascular lesion not confined to the kidney.[4] For not uncommonly patients with minimal renal involvement, as evidenced by albuminuria and hematuria, present the severest degree of cardiac insufficiency, which may even lead to death. Furthermore, hypertension or edema may be the initial sign of the disease, indicating a universal vascular disturbance. On the assumption, therefore, that organic changes are present in the heart, we took repeated electrocardiograms in cases of acute nephritis several years ago. Striking abnormalities were encountered, and a preliminary report was made.[5] Subsequently

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From the Cardiographic Laboratory and the Medical Services, the Mount Sinai Hospital.

The investigation was aided by funds donated by Mrs. Charles Altschul, Mr. Frank Altschul and Mr. Herbert H. Lehman.

1. Goodhart, J. F.: On Acute Dilatation of the Heart as a Cause of Death in Scarlatinal Dropsy: Five Cases, Guy's Hosp. Rep. **24**:158, 1879.

2. Volhard, F., and Fahr, T.: Die Brightische Nierenkrankheit, Berlin, Julius Springer, 1914, p. 118.

3. Levy, I. J.: The Cardiac Response in Acute Diffuse Glomerulo-Nephritis, Am. Heart J. **5**:277, 1930.

4. Fishberg, A. M.: Hypertension and Nephritis, ed. 1, Philadelphia, Lea & Febiger, 1930, p. 320.

5. Master, A. M.; Jaffe, H. L., and Dack, S.: The Electrocardiogram in Acute Nephritis, Am. Heart J. **12**:244, 1936.

several European authors studied the heart in this disease. Marcolongo [6] observed cardiac dilatation in every patient investigated roentgenographically when hypertension was present. Alsina-Bofill [7] found dyspnea a constant symptom in these patients. Twenty per cent of the patients studied by Ellis [8] exhibited cardiac insufficiency. In thirteen patients followed electrocardiographically as well as clinically Tur [9] independently observed changes in the T wave similar to those found by us. Langendorf and Pick [10] also reported abnormalities in the T wave in thirteen patients. The T wave became inverted in leads I and II and upright in lead IV; simultaneously the T_3 became pointed. The authors were impressed with the specificity of the changes and the simulation of the electrocardiogram obtained in anterior infarction.

The present report attempts to correlate the electrocardiographic changes with the clinical course in acute glomerulonephritis (table 1). It is based on a study of twenty-four patients with typical involvement for whom electrocardiograms were taken at frequent intervals, the average number being seven. The series is not consecutive, for patients with only occasional records have been excluded; hence our results do not express quantitative relationships. In almost all cases precordial leads were taken in addition to the three standard limb leads; a few patients were studied prior to the introduction of the use of the precordial lead.

The following report will serve to illustrate the characteristic clinical and electrocardiographic findings:

R. W., a Negro porter *27* years of age, had an unimportant previous history except for gonorrhea. Four weeks before admission to the hospital he contracted an infection of the upper respiratory tract which lasted two days. He felt well for a week, until he suddenly became dyspneic while attempting to push a cart. This symptom disappeared after rest but recurred several days later when he was walking. Thereafter he suffered frequent attacks of nocturnal dyspnea and was unable to climb one flight of stairs. He complained also of weakness and palpitation. One week after the onset of dyspnea the urine became darker. However, he continued to work for several weeks, until he noticed swelling of the legs and puffiness of the eyelids and the dyspnea became severe.

On admission to the hospital the patient was acutely dsypneic and orthopneic and moderately cyanotic. The eyelids were puffy. The arteries of the fundus were of normal caliber. The tonsils were injected. Moist râles were present at

6. Marcolongo, F.: Il cuore nella glomerulonefrite acuta diffusa, Arch. per le sc. med. **59**:975, 1935.

7. Alsina-Bofill, J.: El corazón en la glomérulonefritis aguda, An. de med. int. **4**:1035, 1935.

8. Ellis, A. W. M.: Heart Failure in Acute Nephritis, Quart. J. Med. **5**:533, 1936.

9. Tur, A.: Electrocardiographic Studies in Acute Diffuse Glomerulonephritis, Klin. med. **13**:1372, 1935.

10. Langendorf, R., and Pick, A.: Elektrokardiogramm bei akuter Nephritis, Med. Klin. **33**:126, 1937.

the base of each lung. The heart was enlarged to the left, the apical impulse being forceful and palpable in the sixth interspace, 1 cm. to the left of the midclavicular line. There was gallop rhythm at the apex, and the sounds were of poor quality. The second pulmonic sound was accentuated and louder than the second aortic

TABLE 1.—*The Heart in Nephritis*

Case	Age	Highest Blood Pressure, Mm. of Hg	Cardiac Symptoms	Lungs	Heart	Electrocardiographic Findings
1	27	190/100	.....	.....	S_1 split; systolic murmur	T_3 inverted; T_2 flat; wide P wave
2	32	180/ 90	Dyspnea; orthopnea	Pleural effusion	Gallop; $P_2>A_2$; mitral configuration	Preponderance of left ventricle
3	15	134/100	Dyspnea; orthopnea	Pulmonary edema	Enlarged to left; $P_2>A_2$; S_1 booming	T_1 cove-plane; T_2 inverted
4	27	200/140	Dyspnea; orthopnea; cyanosis	Râles	Enlarged to left; gallop; poor sounds; $P_2>A_2$	T_1 cove-plane; T_2 inverted; T_4 upright and pointed; P wave notched and high; absent initial positive deflection
5	32	190/130	.....	.....	S_1 split; $P_2>A_2$	T_1 inverted; T_2 semi-inverted
6	15	176/ 96	.....	.....	$P_2>A_2$	T_1, T_2 and T_3 high and pointed; PR, 0.22 second
7	39	160/105	Dyspnea	.....	$P_2>A_2$	T_1 and T_2 low
8	28	150/ 94	.....	.....	Poor sounds	PR, 0.24 second; P wave wide and notched
9	37	168/106	.....	.....	.....	No abnormality
10	34	160/108	Dyspnea	.....	.....	T_1, T_2 and T_4 high and pointed; PR, 0.22 second
11	14	176/110	.....	.....	Enlarged	T_1 low; PR, 0.2 second
12	31	150/ 90	.....	.....	.....	T_1 low; T_2 semi-inverted; T_4 diphasic
13	41	180/100	Dyspnea	Pulmonary edema	Enlarged; gallop sounds split; $P_2>A_2$	T_1 low; T_2 iso-electric; T_4 upright; PR, 0.2 second
14	14	142/ 74	.....	Pleural effusion	$P_2>A_2$	T_1 and T_2 diphasic
15	32	148/ 98	.....	.....	.....	No abnormality
16	40	170/ 60	Dyspnea; orthopnea	Pulmonary edema	Enlarged	Auricular flutter; T_1 diphasic; T_2 inverted
17	29	130/ 92	.....	.....	Enlarged	T_1 low; T_2 semi-inverted; T_4 diphasic
18	24	184/106	.....	.....	$P_2>A_2$	T_2 low; T_4 diphasic; P wave high and notched
19	15½	160/100	.....	.....	Enlarged; $P_2>A_2$	T_1, T_2 and T_4 high and pointed; Q_1 present; small initial positive deflection
20	13	142/ 80	.....	.....	S_1 split	T_1 low
21	40	156/ 80	.....	.....	.....	T_1 pointed
22	45	170/ 90	Dyspnea; orthopnea	Pulmonary edema	.....	Preponderance of left ventricle
23	40	200/100	Dyspnea; orthopnea	Pulmonary edema	.....	T_1 and T_4 low; initial positive deflection absent
24	17	150/ 90	.....	.....	Enlarged	No abnormality

sound. The heart rate was 110, and the blood pressure was 200 systolic and 140 diastolic. There was pitting edema of the legs. The venous pressure measured 6 cm. of water, the arm to tongue circulation time was twenty-two seconds and the vital capacity was 1,600 cc.—evidences of isolated failure of the left ventricle.

The urine contained 3 plus albumin and numerous red blood cells and casts. The urea nitrogen content of the blood was 14 mg. per hundred cubic centimeters.

Phlebotomy was performed, and the patient was allowed neither fluids nor food. Improvement was rapid; by the next day the dyspnea, râles in the lungs, tachycardia and gallop rhythm had disappeared. He continued to do well, the heart became smaller and the blood pressure returned to normal. The arm to tongue circulation time diminished to sixteen seconds, and the vital capacity rose to 2,750 cc. On the thirteenth day, however, the blood pressure suddenly rose to 150 systolic and 100 diastolic, the heart began to enlarge again, the apical sounds became poor, a rough systolic murmur was heard over the pulmonic area and the second pulmonic sound became accentuated. There were numerous premature beats. With limitation of fluids, all these signs disappeared in one day, and the patient went on to complete recovery.

When the patient was admitted to the hospital the electrocardiogram (fig. 1, Dec. 18) showed sinus tachycardia, preponderance of the left ventricle, a prominent notched P wave, slight slurring of the QRS complex, absence of the initial positive deflection in the precordial lead and low voltage of the T wave. Five days later the rate was slower, and there was no preponderance. The initial positive deflection had reappeared. Wave T_1 was inverted and cove-plane, T_2 slightly inverted and T_4 deeply negative and pointed. The changes in the T wave were similar to those seen in anterior infarction. Ten days later preponderance of the left ventricle was again present, waves T_1 and T_4 were diphasic and wave T_3 was upright.

Comment.—In summary, this patient with acute glomerulonephritis presented for several weeks only evidence of failure of the left ventricle, that is, increasing dyspnea and hypertension. Signs of renal disease appeared later. On admission to the hospital he showed signs of advanced insufficiency of the left ventricle, associated with which were changes in the electrocardiogram indicative of myocardial damage. With active treatment the failure of the left ventricle rapidly disappeared, except for a transient recurrence. The changes in the electrocardiogram became more definite but had begun to regress before he was discharged. Although there was severe involvement of the myocardium from the onset, at no time was there evidence of more than moderate renal impairment.

CLINICAL DATA

The majority of the twenty-four patients were young adults, the average age being 27, and the range from 13 to 45 years. The sexes were almost equally represented.

In two thirds of the patients an infection of the upper respiratory tract, usually tonsillitis, preceded the onset of the acute nephritis. The latter was usually evidenced by hematuria and edema, but in two patients the initial symptom was severe dyspnea, so that primary cardiac disease was simulated. In four other patients dyspnea was a prominent and early complaint. These findings confirm the observations of Baehr [11] that symptoms of heart failure often occur early in the course of acute glomerulonephritis, before there is extensive renal damage.

11. Baehr, G.: Personal communication to the authors.

In the examination of these patients a constant finding was systolic and diastolic hypertension, the highest reading being 200 systolic and 140 diastolic (table 1). The slightest elevation of blood pressure, 142 systolic and 80 diastolic, was obtained for a boy of 13; at this age such a reading is definitely abnormal. In each case the hypertension was already present when the patient was first observed. Hypertension is one of the earliest signs. In several cases the blood pressure dropped quickly; more often it returned to a normal level by the end of the first

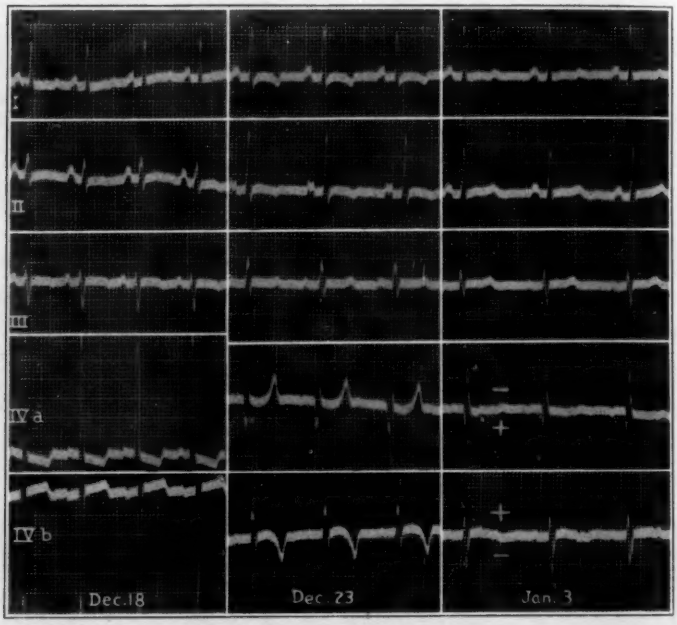

Fig. 1 (case 4, a man aged 27).—Dec. 18: Sinus tachycardia; pulse rate, 110; preponderance of the left ventricle; wide and prominent P wave; slurring of QRS; practically iso-electric T wave; initial positive deflection absent in the chest lead. In this and the succeeding figures lead IV *a* is the chest lead in which waves of positive polarity are directed downward and lead IV *b* is the chest lead arranged so that positive waves are directed upward. Dec. 23: Pulse rate, 80; no preponderance of left ventricle; the voltage of the QRS complex is higher; P wave, notched; T_1, inverted and cove-plane; T_2, semi-inverted; T_3, upright. In the chest lead the initial positive deflection is present; the T wave is of negative polarity. Jan. 3: Preponderance of the left ventricle is again present. P wave, no longer notched; T_1, becoming upright; T_2 and T_3, normal; T_4, iso-electric.

or second week, but in five patients it was still at the upper limit of normal on discharge, when recovery was otherwise complete. Associated with the hypertension in one third of the patients was moderate

enlargement of the heart to the left, as determined by percussion. This figure is undoubtedly too small, for few of the patients were examined roentgenologically. As the blood pressure fell the size of the heart diminished (fig. 2). Other evidence of cardiac involvement included a systolic murmur in nine patients, which usually disappeared, and frequently alterations in the heart sounds, which were booming, poor or split for varying periods.

In addition to these findings, eight patients presented definite evidence of failure of the left ventricle, that is, dyspnea and orthopnea, gallop rhythm, accentuated second pulmonic sound, pulmonary congestion and, in five instances, pulmonary edema. Furthermore the vital capacity was considerably reduced in two patients tested, and in one of these the arm to tongue circulation time was prolonged. Pulmonary edema was usually sudden in onset and severe. In several cases death

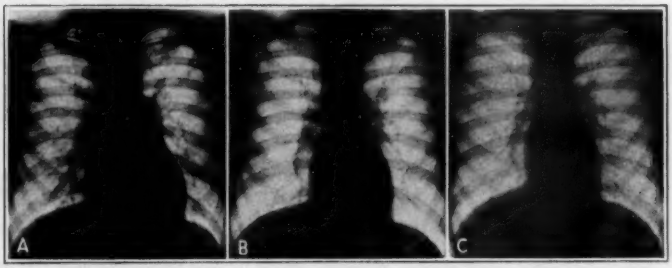

Fig. 2 (case 24, a boy aged 17).—Cardiac enlargement during the first week of acute nephritis; progressive diminution in size to normal; elevation of blood pressure until March 2; normal thereafter, ranging between 120 systolic and 80 diastolic and 106 systolic and 70 diastolic; normal electrocardiogram. *A* was taken on March 1; *B*, on March 8, and *C*, on March 26.

seemed imminent and was averted only by prompt treatment. The edema occurred only during the stage of hypertension, that is, early in the course of the disease. In two patients it recurred.

Contrary to the statement of Levy [8] that failure of the right ventricle is primary, in none of our patients was there unequivocal clinical evidence of this failure, such as dilatation of the veins of the neck or enlargement of the liver. Nor is this surprising, since hypertension increases the work of the left ventricle alone. The significance of edema, ascites or pleural effusion, findings usually indicative of failure of the right ventricle, was necessarily difficult to determine for our patients. However, these features were probably largely the result of the disturbance of water metabolism due to the systemic capillary injury and not to heart failure, for the highest venous pressure reading obtained was 9 cm. in four cases. This figure is the upper limit of normal and is not sufficiently high for a definite diagnosis of heart failure. This

interpretation is even more probable in view of the fact that in two of the patients with a venous pressure of 9 cm. there was no other evidence of heart failure. Furthermore, for the patients with the most advanced degree of failure of the left side of the heart the venous pressure was normal, as in the case cited.

There were two fatal cases in this series, and in both instances there was failure of the left ventricle. One of these patients was a girl of 14 who was apparently recovering when she died suddenly on the twelfth day. The other was a man of 40 with long-standing rheumatic cardiovalvular disease who showed a progressively downhill course. He died in uremia; postmortem examination revealed no evidence of acute myocardial or endocardial disease.

ELECTROCARDIOGRAPHIC FINDINGS

The electrocardiogram was significantly abnormal at some period of the disease in nineteen patients, in three no change occurred and in the

TABLE 2.—*Electrocardiographic Changes in Nephritis*

	Number of Cases	
Sinus tachycardia	7	
Sinus bradycardia	3	
Ventricular premature beats	1	
Auricular premature beats	2	
Auricular flutter	1	
Abnormalities of P wave	4	
Prolonged PR interval	5	(longest, 0.24 second)
Preponderance of left ventricle	9	(3 transient)
Low voltage of QRS	5	(2 transient)
High voltage of QRS	2	
Slurring of QRS	6	(2 transient)
Large Qa present	3	(did not change)
Absent initial positive deflection in chest lead	3	(2 became small; 1 normal)
RT elevated	2	(slight)
T wave high and pointed	4	
T wave low	4	
T wave iso-electric to inverted	10	

remaining two preponderance of the left ventricle alone appeared soon after observation. As will be seen in table 2, the chief abnormalities involved the T wave and, to a less extent, the auriculoventricular conduction time (PR interval) and the initial positive deflection in the precordial lead. Except for premature beats, the only significant arrhythmia was a single instance of auricular flutter. Several authors [12] have emphasized the frequency of bradycardia during the acute stage; we observed this in only a minority of patients. It is true that the pulse rate did not rise above 110 unless there was severe failure of the left side of the heart. Preponderance of the left ventricle was present in nine patients, but in only three did this appear or disappear while they were under observation (fig. 1). Low or high voltage and slurring of

12. Marcolongo.[6] Alsina-Bofill.[7]

the QRS complex were encountered frequently (figs. 3) but often were constant. In one of five patients with prolongation of the PR interval this was the only abnormality in the electrocardiogram. The longest interval was twenty-four hundredths of a second. In three cases the PR interval returned to normal, in the remaining two it became shortened but persisted at from one fifth to twenty-two hundredths of a second. In four cases the P wave was high, wide or notched (figs. 1 and 4 *A*). This was interpreted as evidence of failure of the left ventricle with dilatation of the auricles.[13]

The abnormalities in the T wave, however, were most striking, occurring in eighteen patients. There were two types of changes. In

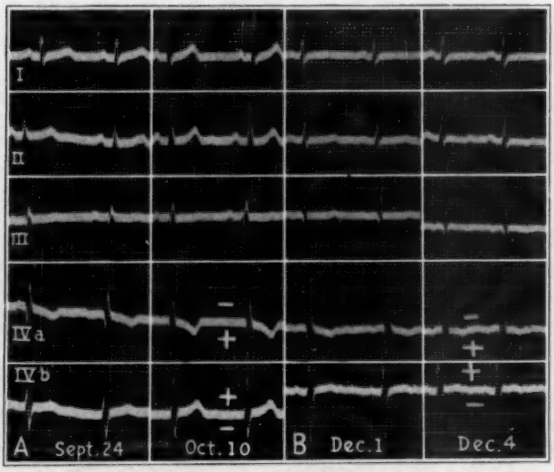

Fig. 3.—*A*, case 15, a woman aged 32. Sept. 24: Low voltage and slurring of the QRS complex in all leads. Oct. 10: QRS complex of normal voltage; higher T wave. *B*, case 20, a girl aged 13. Dec. 1: QRS complex and T wave of low voltage. Dec. 4: Slightly higher voltage of QRS; T_3, semi-inverted.

four patients the T wave became large and pointed (fig. 4 *A*); in fourteen it became low or, more often, inverted. The changes were often progressive, frequently from day to day. In the ten patients who went on to inversion of the T wave, as in the case outlined, a close similarity to the sequence in myocardial infarction could be noted, especially when the T wave was cove-plane; definite RT abnormalities, however, were lacking. The simulation of infarction was enhanced by the fact that the changes occurred in the first and second leads, as in involvement

13. Master, A. M.: P-Wave Changes in Acute Coronary Artery Occlusion. Am. Heart J. **8**:462, 1933.

of the anterior surface of the heart (figs. 1, 4 *B* and 5). It should be remembered that other conditions produce similar changes. In the majority of patients, however, the changes, though definite, were less characteristic; the T waves in leads I and II, less commonly in the first lead alone, became iso-electric or small (fig 3 *B*). Changes in the T_3 wave were usually slight and of doubtful significance; the pointed T_3 wave noted by Langendorf and Pick [10] was not observed. Regression of the changes was often gradual, requiring one or two weeks for complete disappearance; in some cases the T wave was still small when the

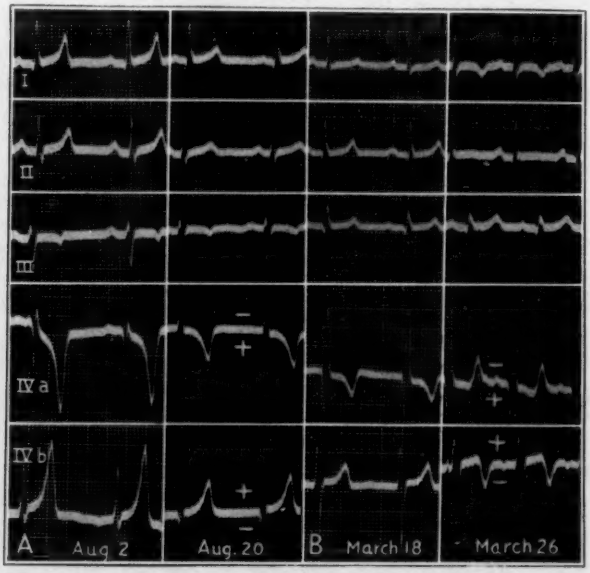

Fig. 4.—*A*, case 10, a man aged 34. Aug. 2: Waves T_1, T_3 and T_4, pointed and of high voltage; preponderance of the left ventricle and slurring of the QRS complex; PR interval, twenty-one hundredths to twenty-two hundredths of a second. Aug. 20: Eighteen days later; T wave of normal voltage; smaller P wave; PR interval, eighteen hundredths of a second. *B*, case 13, a man aged 41. March 18: Normal record except for slight slurring of the QRS complex. March 26: Wave T_1, inverted and cove-plane; T_3, iso-electric; T_4, of negative polarity.

patients were discharged. These changes almost always outlasted the clinical symptoms.

It is interesting to note that changes frequently occurred also in the precordial lead. In our series an abnormal T_4 wave (negative or less than 1 mm.) occurred five times, always in association with inversion of the T wave in the standard leads (figs. 1, 4 *B* and 5). Another significant change, which was not present in the patients reported on

by Langendorf and Pick,[10] was the absence of the initial positive deflection in three patients (fig. 1). Heretofore this finding has been associated by most authors with anterior infarction. Hence the typical electrocardiographic picture of the anterior infarction may be simulated in acute nephritis when waves T_1 and T_2 are inverted, the initial positive deflection is absent and the T_4 wave is of negative polarity. In all three patients absence of the initial positive deflection was transient; in one it became normal, but in the other two it remained small (2 mm. or less). In a study to be published [14] it has been shown that an initial positive

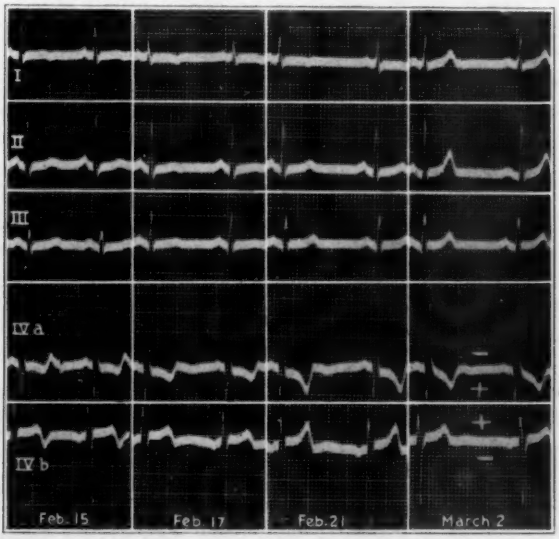

Fig. 5 (case 5, a man aged 32).—Feb. 15: Wave T_1, semi-inverted; T_4, diphasic. Feb. 17: T_2, semi-inverted. Feb. 21: T_3, upright; T_4, normal. March 2: Normal T wave in all leads.

deflection of this size is usually abnormal and that changes in this wave may occur in the absence of infarction.

An attempt was made to correlate the presence of cardiac involvement with changes in the electrocardiogram. This was not always successful; thus two of the eight patients with definite evidence of failure of the left ventricle presented normal electrocardiograms. The remaining six, however, showed striking changes in the T wave and twice the initial positive deflection was absent; in none of these patients was the

14. Master, A. M.; Dack, S.; Kalter, H., and Jaffe, H. L.: The Significance of an Absent or Small Initial Positive Deflection in the Precordial Lead, Am. Heart J. **14**:297, 1937.

PR interval prolonged. Nor were the changes in the electrocardiogram always coincident with the presence of hypertension or cardiac insufficiency. In the majority of patients they appeared later and remained when the blood pressure had returned to normal. It is notable, furthermore, that in one case death occurred after the electrocardiogram had become normal.

COMMENT

Hypertension is the rule in acute glomerulonephritis. Cardiac insufficiency is common and at times is severe enough to cause death. It has usually been assumed that the failure depended directly on the rise in blood pressure and represented the inability of the left ventricle to cope with the sudden increased peripheral resistance. This explanation, however, does not seem to hold in most cases. In several patients with cardiac failure the blood pressure did not rise much; thus while it reached 200 mm. in two instances, the average elevation was only to from 150 to 160 mm. Furthermore, this elevation was always temporary; indeed, as we have seen, the blood pressure frequently returned to normal in a week. It is unlikely that a heart of normal structure would fail in the presence of such a transient and moderate increase in work. Failure does not occur, for example, as a result of the sudden elevation in pressure associated with tumor of the adrenal medulla or with lead poisoning.

These clinical considerations lead, therefore, to the conclusion that in acute glomerulonephritis the heart, as well as the kidneys and other organs, is involved in a universal vascular lesion. The latter involves the smaller vessels diffusely, giving rise almost uniformly to some increase in blood pressure at the onset of the disease. This is independent of renal involvement. In many cases, furthermore, the injury to the heart is severe enough to produce profound changes in the electrocardiogram, usually considered indicative of diffuse cardiac damage, including the myocardium (QRS and T waves) and the conduction system (PR interval). The objection may be raised that the inversion of the T wave in leads I and II in our patients was produced by a change in size and shape of the left ventricle consequent to the hypertension and did not represent actual injury to the heart. The influence of the configuration of the heart on the electrocardiogram has been stressed.[15] Yet this would not account for the prolongation of the PR interval or for the appearance or persistence of the changes after the hypertension and cardiac dilatation have disappeared. Hence both the

15. Master, A. M.: Characteristic Electrocardiograms and Roentgenograms in Arterial Hypertension, Am. Heart J. **5**:291, 1930; Right Ventricular Preponderance (Axis Deviation) of the Heart, Am. J. M. Sc. **186**:714, 1933. Barnes, A. R.: The Clinical Significance of Certain Abnormalities of the T-Wave in the Electrocardiogram, Proc. Staff Meet., Mayo Clin. **8**:54 (Jan. 25) 1930.

electrocardiographic abnormalities and the myocardial insufficiency seem to bespeak actual myocardial changes. It was therefore surprising not to observe gross anatomic or significant microscopic changes in routine sections of the hearts of six patients outside of our series as well as in sections of the heart of one patient in our series, who was examined post mortem at this hospital by Dr. Paul Klemperer. Several showed edematous infiltration of the musculature of the heart; in one patient who showed clinical signs of severe failure of the left side of the heart the process was advanced enough to be termed serous myocarditis, for there were, in addition, numerous small foci of infiltration with lymphoid cells. The exact significance of these changes is not certain. However, the usual mechanism of the formation of edema in general is capillary damage, and this may be presumed to hold in these cases, despite the impossibility of demonstrating this change morphologically. It is noteworthy that Stone [16] reported one instance of arteriolitis of the heart in acute nephritis, as well as in other organs in other cases. The absence of visible microscopic changes in the capillaries in these cases does not preclude the possibility of capillary derangement, toxic or chemical in nature. In acute glomerulonephritis there is a profound physiologic alteration of the tissue fluids and electrolytes, as evidenced by edema, which is almost invariably observed in the skin and not infrequently in the brain. It is not unlikely that the internal organs, including the heart, are affected similarly. The myocardial injury which follows accounts for the electrocardiographic changes reported, and if a marked elevation in blood pressure occurs and the damaged heart is unable to cope with the increased work, heart failure ensues.

SUMMARY

Acute glomerulonephritis is sometimes associated with clinical symptoms of failure of the left ventricle, such as, dyspnea, cyanosis and pulmonary edema. These appear early in the course of the disease; in fact, they may be the presenting symptoms and may occur before there is evidence of renal injury. The involvement of the heart is the result of vascular and not renal damage.

The diffuse vascular change also produces hypertension, which is almost always present in the first week or two of the disease.

Changes occur in the electrocardiogram which indicate myocardial damage, that is, definite abnormalities of the T wave in leads I, II and IV, absence of the initial positive deflection in the precordail lead and prolongation of the auriculoventricular conduction time.

Acute glomerulonephritis is a systemic vascular disease in which the heart may be seriously damaged.

16. Stone, W. J.: Bright's Disease and Arterial Hypertension, Philadelphia, W. B. Saunders Company, 1936.

RENAL FUNCTION IN OBSTRUCTIVE JAUNDICE

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Obstructive jaundice produces anatomic changes in the kidneys consisting chiefly of degeneration of the tubular epithelium, long familiar to pathologists under the name cholemic nephrosis. The resulting disturbances in renal function, although recognized by clinicians, have received relatively little recent study. In the present report are given the observations made on a group of patients with obstructive jaundice on whom tests of renal function were employed in an effort to delineate more carefully the clinical features of the renal lesion and to determine the severity and the course. The results indicate that clinically detectable jaundice is invariably associated with the appearance of rather characteristic abnormalities of the urine and frequently with decreased renal function. The evidence of the renal lesion disappears promptly as the jaundice subsides, leaving no detectable sign of residual damage.

METHODS OF STUDY

The subjects of the investigation were sixteen patients suffering from obstructive jaundice and one patient with arsenical hepatitis admitted to the medical or surgical wards of the University Hospital. Only those patients were selected for whom it was possible to rule out preexisting renal disease with reasonable certainty. There were ten males and seven females, their ages ranging from 7 to 74 years. Renal function was tested by the method of Addis.[1] Urine was collected for twelve hours, and the formed elements in a measured portion were enumerated. Protein precipitated from a filtered sample of urine by acetic acid was measured gravimetrically. The formed elements and protein excreted in twelve hours were calculated. Urea clearance was determined, the sample of blood being obtained at the end of a twelve hour collection of urine.[2] No attempt was made to determine the concentrating power of the kidneys, since in many cases it seemed inadvisable to restrict the intake of fluid. A quantitative van den Bergh estimation was carried out on the day the renal function was tested.

The expense of this investigation was in large part defrayed by a grant from the Commonwealth Fund.

From the Gastro-Intestinal Section and the Renal Section of the Medical Clinic, the University of Pennsylvania Hospital.

1. Addis, T., and Oliver, J.: The Renal Lesion in Bright's Disease, New York, Paul B. Hoeber, Inc., 1931.

2. Landis, E. M.; Elsom, K. A.; Bott, P. A., and Shiels, E.: Observations on Sodium Chloride Restriction and Urea Clearance in Renal Insufficiency, J. Clin. Investigation **14**:525, 1935.

RESULTS

The results are given in the accompanying table. It is apparent that in every patient the urinary sediment was abnormal and that the deviations from normal were qualitatively consistent (chart 1). The outstanding abnormality was the increased excretion of casts, which in some patients were present in enormous numbers. The casts were usually either small and coarsely granular or hyaline, and adherent to them were bile-stained renal epithelial cells. A less striking but equally consistent abnormality was the increased number of epithelial cells and leukocytes, most of which were deeply bile stained. It is believed that

Data for Seventeen Patients

Case	Age	Clinical Diagnosis	Van den Bergh Units	Addis Sediment Count: Casts, Thousand per 12 Hr.	Addis Sediment Count: Epithelial and White Blood Cells, Million per 12 Hr.	Addis Sediment Count: Erythrocytes, Million per 12 Hr.	Blood Urea Nitrogen, Mg. per 100 Cc.	12 Hour Urea Clearance, % of Normal	Protein Excretion, Mg. per 12 Hr.	Plasma Protein, Gm. per 100 Cc.
		Normal	....	5	2.00	0.50	15.0	...	100	...
1	33	Carcinoma of pancreas	27.0	80	8.00	0.11	6.6	74	0	5.0
2	7	Catarrhal jaundice	24.0	2,224	3.20	0.00	12.8	107	250	9.0
3	72	Choledocholithiasis	24.0	457	19.00	0.79	12.4	113	0	...
4	62	Carcinoma of liver	24.0	209	3.60	1.30	12.8	68	0	5.7
5	52	Carcinoma of pancreas	24.0	541	2.60	0.48	15.5	48	130	...
6	32	Obstruction of common duct	24.0	198	9.00	0.23	....	...	400	...
7	49	Carcinoma of stomach	20.4	124	7.60	2.30	20.3	48	17	4.5
8	39	Calculous cholecystitis	18.4	205	6.30	0.25	8.2	66	30	...
9	32	Arsenical hepatitis	16.0	233	2.80	2.30	5.6	104	30	...
10	48	Undetermined	15.0	345	12.30	0.44	8.1	68	0	...
11	36	Hepatic cirrhosis	14.4	120	11.00	40.00	18.8	35	0	6.1
12	53	Stenosis of common duct	13.0	49	2.60	0.30	5.4	96	0	6.9
13	46	Carcinoma of gallbladder; metastasis to liver	11.0	302	11.00	2.20	28.1	70	300 19	5.0 6.7
14	67	Choledocholithiasis	7.3	157	17.00	139.00	20.6	30	...	...
15	39	Catarrhal jaundice	4.8	42	2.20	0.90	19.8	57	0	...
16	74	Cholecystitis	4.0	11	1.30	0.10	10.0	48	40	...
17	56	Calculous cholecystitis	3.7	30	0.94	1.00	16.1	23	20	...

they were derived from the renal epithelium and were not simply extrarenal cells stained by the urine in which they were immersed. Some of the epithelial cells contained the pigment granules described by Haessler, Rous and Broun.[3] Irregular extracellular particles, which these authors found gave an intense Gmelin reaction, were observed in the sediment. As in the true nephrotic syndrome, the number of red blood cells excreted was conspicuously small. In nine patients the erythrocyte count was within normal limits, in six others it was moderately increased and in only two was it significantly increased. Albuminuria was even less conspicuous. Thirteen of the seventeen patients excreted no more

3. Haessler, F. H.; Rous, P., and Broun, G. O.: The Renal Elimination of Bilirubin, J. Exper. Med. **35**:533, 1922.

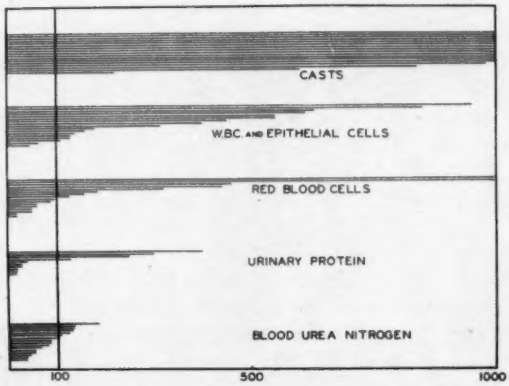

Chart 1.—The abnormalities in the urinary sediment. Each line represents the value for a single patient, given in percentage of normal. The greatest number of casts excreted was 44,000 per cent of the normal figure.

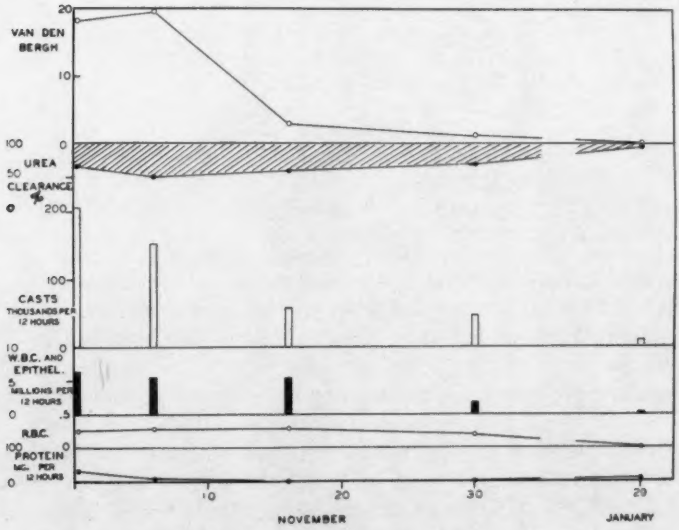

Chart 2.—The subsidence of the renal lesion in one patient (case 8).

protein than do normal persons, and the remaining four excreted only slightly more than normal. It is this fact which sharply distinguishes the present disorder from the usual clinical forms of nephrosis, for, as one would anticipate, no one of the patients described here had demonstrable edema or the other clinical features of the nephrotic syndrome. The estimation of the protein content was carried out on a filtered sample of urine, which therefore was free from casts and cells. It is worthy of notice that these elements contribute an amount of protein to the urine which is insignificantly small, judged by an analysis of the urine of the patient (case 2) for whom the highest number of casts was observed. The amount of protein excreted in twelve hours was 267 mg. in unfiltered urine and 250 mg. in filtered urine, a difference almost within the limits of error of measurement in a 10 cc. sample. The value for the urea nitrogen content of the blood was normal in most instances; the highest figure recorded was 28 mg. per hundred cubic centimeters. The urea clearance of the group as a whole was extremely variable, being significantly [4] decreased in only half the subjects.

Repeated observations of several subjects during recovery from the jaundice yielded data of interest concerning the course of the renal lesion. In each patient the evidence of the renal damage disappeared *pari passu* with the icterus. In one subject (chart 2, case 2) the renal function promptly returned to normal as the jaundice disappeared. Eight weeks after the height of the disease the urinary sediment was entirely normal, and the urea clearance, which had been 50 per cent of normal, had returned to normal.

COMMENT

The term cholemic nephrosis implies that there is renal damage due to some of the constituents of retained bile. The recent demonstration of Stewart and Cantarow [5] that bile salt (sodium dehydrocholate) may produce in the kidneys of animals degenerative lesions similar to those which constitute the pathologic picture of cholemic nephrosis greatly strengthens this implication. It would be unwarranted on this ground alone, however, to attribute the renal damage solely to the retention of bile, for in biliary obstruction there also occurs damage to the hepatic cells which may result in the production of other nephrotoxic sub-

4. Standards for normal have not been fully worked out for the twelve-hour urea clearance without restriction of fluids. In the present study the lower limit has been somewhat arbitrarily set at 80 per cent of normal.

5. Stewart, H. L., and Cantarow, A.: Renal Lesions Following Injection of Sodium Dehydrocholate in Animals With and Without Biliary Stasis, Arch. Path. **20**:866 (Dec.) 1935.

stances.[6] This is borne out by clinical reports [7] in which renal insufficiency has occurred in patients with hepatic disease not associated with jaundice. In these cases it was assumed that injury to the liver resulted in the elaboration of nephrotoxic substances, probably protein in nature. Attempts to produce these substances in animals by reduction of the hepatic blood supply, trauma to the liver and extraction of hepatic tissue by various methods have been partially successful, but the exact nature of the substances so produced is not known.[8] The present study provides no data concerning the relative parts played by various factors presumed to produce the renal damage, such as retained bile salt and hepatic nephrotoxins. The fact that three patients who had conspicuous renal damage also showed normal tolerance to galactose inclines one, however, to regard the products of hepatic damage as a less important cause of renal injury than the retained bile, although this must remain a matter of conjecture until more delicate tests of hepatic function are developed.

It is of interest to examine the clinical evidence of renal damage in the light of the histologic changes known to occur in the kidneys of jaundiced patients. These are degenerative rather than inflammatory, varying in degree from simple cloudy swelling to complete necrosis of the tubular epithelium. There is a variable amount of cellular débris, bile pigment and albuminous material in the lumens of the tubules, which are sometimes obstructed and widely dilated. The glomeruli, as in other forms of nephrosis, appear to be relatively normal.[9] The presence in the urinary sediment of large numbers of casts, renal epithelial cells and leukocytes and the striking absence of erythrocytes are the findings one would anticipate in a noninflammatory desquamative pathologic process within the kidneys. The transient reduction in the urea clearance may be due to the temporary damage to the tubular epithelium, through which an abnormally great back-diffusion of urea occurs, such as is thought to take place in mercury bichloride poisoning. The glomeruli, which appear to be anatomically normal, maintain their

6. Lichtman, S. S., and Sohval, A. R.: Clinical Disorders with Associated Hepatic and Renal Manifestations, with Special Reference to the So-Called "Hepatorenal Syndrome," Am. J. Digest. Dis. & Nutrition **4**:26, 1937.

7. (*a*) Helwig, F. C., and Schutz, C. B.: A Liver Kidney Syndrome: Clinical, Pathological, and Experimental Studies, Surg., Gynec. & Obst. **55**:570, 1932. (*b*) Fitz-Hugh, T., Jr.: Hepato-Urologic Syndromes: Obstructive Jaundice and Nephritis; Urologic Infections and Cholemia, M. Clin. North America **12**:1101, 1929.

8. Boyce, F. F., and McFetridge, E. M.: So-Called "Liver Death": A Clinical and Experimental Study, Arch. Surg. **31**:105 (July) 1935. Helwig and Schutz.[7a]

9. Wilbur, D. L.: The Renal Glomerulus in Various Forms of Nephrosis, Arch. Path. **18**:157 (Aug.) 1934.

impermeability to protein, so the reduction of plasma protein that is sometimes observed is not the result of a loss of protein. It should be emphasized that the term cholemic nephrosis is descriptive of the pathologic changes within the kidneys and does not signify the presence of the nephrotic syndrome considered in the clinical sense.

In no one of the patients described here was the disturbance in renal function of serious clinical significance. Nor does it seem likely, in view of the prompt disappearance of all evidence of renal damage, that the kidneys sustained permanent injury which might later become manifest. While in most instances the renal disturbance incident to jaundice is probably a matter of less concern than the underlying disease, it may assume a rôle of dominant importance, particularly if surgical treatment is undertaken. Walters and Parham,[10] Wilbur,[9] Rowntree [11] and Bartlett [12] have described cases in which renal insufficiency followed operations for the relief of biliary obstruction. Of the twenty-one acutely ill, jaundiced patients described by Meyers, Brines and Juliar,[13] five whose kidneys showed no other pathologic changes than those of cholemic nephrosis had renal failure. In one of Fitz-Hugh's [7b] patients incipient uremia threatened life but completely disappeared when the jaundice had subsided after cholelithotomy. The disturbance in renal function incident to jaundice may therefore become a matter which greatly influences the practical management of patients with biliary obstruction; hence its degree and course should be carefully assessed.

SUMMARY

Sixteen patients with obstructive jaundice and one patient with arsenical hepatitis presented signs of renal damage, consisting chiefly of excessive excretion of casts, epithelial cells and leukocytes. Hematuria and albuminuria were inconspicuous. The urea clearance was frequently reduced. As the jaundice subsided the evidence of renal injury entirely disappeared.

Miss E. H. Shiels performed the chemical analyses included in this report.

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11. Rowntree, L. G.: Certain Clinical and Terminal Pictures in Hepatic Disease, M. Clin. North America **13**:1399, 1930.

12. Bartlett, W., Jr.: Renal Complications of Biliary Tract Infections, Surg., Gynec. & Obst. **56**:1080, 1933.

13. Meyers, S. G.; Brines, O. A., and Juliar, B.: The Acutely Ill, Jaundiced Patient: A Report of Twenty-One Instances of Hepatic Icterus, Seven of Whom Had High Blood Nitrogen, Am. J. Digest. Dis. & Nutrition **2**:346, 1935.

CARDIAC OUTPUT IN HEART DISEASE

DETERMINED BY THE DIRECT FICK METHOD, INCLUDING COMPARATIVE DETERMINATIONS BY THE ACETYLENE METHOD

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CINCINNATI

Contradictory results regarding the output of the heart in congestive failure have been obtained by various indirect methods. These results have led to two distinct ideas regarding the relationship of cardiac output to heart failure: 1. The signs and symptoms of cardiac failure are the result of diminished cardiac output—Mackenzie;[1] Lewis;[2] Meakins and Long;[3] Means;[4] Stewart and Cohn;[5] Blumgart, Riseman, Davis and Berlin,[6] and Henderson, Haggard and Dolley.[7] 2. There is no consistent relationship between cardiac output and heart failure—Harrison[8] and Hamilton, Moore, Kinsman and Spurling.[9]

From the Department of Internal Medicine, the University of Cincinnati.

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4. Means, J. H.: Dyspnoea, Medicine **3**:309, 1924.

5. Stewart, H. J., and Cohn, A. E.: Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart: II. The Effect on the Output of Hearts of Dogs Subject to Artificial Auricular Fibrillation, J. Clin. Investigation **11**:917, 1932.

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The results of indirect methods have been adversely criticized because different methods have given widely varying values. Even the original acetylene method of Grollman,[10] which is generally considered the best of the indirect methods, has been modified by its originator when used for patients with congestive heart failure, as pulmonary congestion and sluggish blood flow greatly impair its reliability.

It seems that a proper evaluation of the acetylene method as modified for use in patients with congestive failure can be determined only by application of the direct Fick method,[11] which Grollman has said "is so direct and unequivocal that the results are open to no possible cavil." We have therefore compared the cardiac output by the direct and the three-sample acetylene method and have in addition studied the cardiodynamics of these patients in order to establish so far as possible the degree of failure of the right and left ventricles in each.

Only three patients with myocardial insufficiency have previously been studied by the direct Fick method. This study was carried out in 1930 by Baumann, Lauter [12] and Friedlander, who reported subnormal values in three cases of cardiac asthma, i. e., 2.3, 3.1 and 3.3 liters per minute. Unfortunately no clinical data concerning the character of the heart disease or the severity of the cardiac asthma in these three patients were included in their report. Shortly thereafter Baumann [13] studied ten normal persons by the direct method and found that the cardiac output ranged between 5.1 and 4.3 liters per minute, the average output being 4.6 liters. Baumann and Grollman [14] employed the direct Fick method in studying patients without evidence of heart disease and compared the results with values obtained by the two-sample acetylene method. A considerable variation in the output of the heart was demon-

10. Grollman, A.: The Cardiac Output of Man in Health and Disease, Springfield, Ill., Charles C. Thomas, Publisher, 1932, p. 206. The rather complicated technic of this method is described in detail by Grollman. The cardiac output is determined by obtaining the oxygen consumption and the arteriovenous oxygen difference.

11. It was first pointed out by Fick in 1870 that the output of the heart can be determined if the following facts are known: (1) oxygen content of the mixed venous blood, (2) oxygen content of the arterial blood and (3) oxygen consumption per minute; e. g., (1) oxygen content of mixed venous blood = 15 volumes per cent, (2) oxygen content of arterial blood = 19 volumes per cent and (3) oxygen consumption per minute = 200 cc. The blood flow through the lungs = $\frac{100}{4} \times 200 = 5$ liters per minute.

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13. Baumann, H.: Ueber die wahre Grösse des Minutenvolumens, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **42**:248, 1930.

14. Baumann, H., and Grollman, A.: Ueber die theoretischen und praktischen Grundlagen und die klinische Zuverlässigkeit der Acetylenmethode zur Bestimmung des Minutenvolumes, Ztschr. f. klin. Med. **115**:41, 1930.

strated, the values ranging from 3.1 to 11.8 liters per minute, but remarkably close agreement was secured when the same patients were examined with the acetylene method. The average cardiac output by the direct method was 6.1 liters per minute and by the acetylene method 6 liters per minute.

In 1930 Klein [15] employed the direct Fick method in man, securing blood from the right side of the heart by introducing a catheter into the right auricle through an antecubital vein. In one normal patient the cardiac output was 4.4 and in a second patient 4.2 liters per minute.

METHOD

For the persons studied by us the determinations were made under basal conditions. The analyses of blood were carried out according to the method and with the apparatus of Van Slyke.[16]

The direct Fick procedure was carried out according to the technic described by Grollman.[10] Arterial puncture was made after collection of mixed venous blood. Grollman's acetylene method, as modified by Grollman and his colleagues [17] to measure the cardiac output of patients with congestive failure, was carried out within forty-eight hours of the time of the direct determination, except for the sixth patient; in this case twenty-eight days elapsed between the determinations. As the clinical condition of this patient remained essentially unchanged, the data regarding the cardiac output are included.

Neither immediate reactions nor subsequent complications were associated with this investigation, but because of theoretical hazards, such as injury to an important coronary vessel or the establishment of serious arrhythmia, we have decided to make no further studies necessitating direct determinations by the Fick method.

For two of the patients studied the diagnosis of pericardial effusion had been made by means of roentgenograms, and the collection of mixed venous blood was a diagnostic procedure. In the other cases permission for the collection of samples was obtained from the patients, who, although suffering from hopeless disease, had become accustomed to painless collection of samples of blood after careful infiltration of the skin with procaine hydrochloride even for simple venous punctures.

For half the patients the direct method preceded the determination by the acetylene method, while the procedure was reversed for the remaining patients. As the relationship between the acetylene and the direct method was consistent, no apparent error was introduced. Acetylene determinations for normal persons were carried out at various times to check the accuracy of our technic. The output for these persons averaged 2.2 liters per square meter of body surface, a value considered by Grollman to be normal.

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15. Klein, O.: Zur Bestimmung des zirkulatorischen Minutenvolumens beim Menschen nach dem Fickschen Prinzip, München. med. Wchnschr. **77**:1311 (Aug. 1) 1930.

16. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 324.

17. Grollman, A.; Friedman, B.; Clark, G., and Harrison, T. R.: Studies in Congestive Heart Failure: XXIII. A Critical Study of Methods for Determining the Cardiac Output in Patients with Cardiac Disease, J. Clin. Investigation **12**:751, 1933.

COMMENT

Brief abstracts of the records of the patients studied will be presented to illustrate the clinical condition of each patient.

The degree of cardiac insufficiency in each patient at the time of the determinations can best be evaluated by examining the accompanying table, where in the majority of cases vital capacity, venous pressure, cardiac size in relationship to thoracic diameter, arterial blood pressure and velocity of blood flow are reported. For all the patients save one (case 2) admission to the hospital was urgently necessitated because of symptoms and signs of myocardial insufficiency; in fact, all except the second and fourth patients had been repeatedly admitted to the hospital because of congestive failure. However, at the time of the determinations of the cardiac output varying degrees of improvement in symptoms and physical findings had resulted from rest, the administration of digitalis and other therapeutic procedures. Consequently the status of cardiac efficiency at the time of the determinations of cardiac output can best be evaluated by a consideration of the measurements of circulatory functions of each patient.

CASE 1.—*Rheumatic heart disease, mitral insufficiency, mitral stenosis, aortic insufficiency and possibly tricuspid insufficiency.*

H. D., a 58 year old night-watchman, was admitted to the hospital for the fifth time, complaining of effort dyspnea of three years' standing, recent precordial pain and edema of the ankles. Physical examination at the time of the determination of the cardiac output showed moderate dyspnea at rest and slight engorgement of the cervical veins. The blood pressure was 122 systolic and 82 diastolic. The pulse was completely irregular, the rate being 50. (An electrocardiogram showed auricular fibrillation, with low voltage of QRS in all leads.) The heart was 19 cm. in diameter in the teleoroentgenogram, with obliteration of the waistline. There was a loud systolic and a softer mid-diastolic murmur at the cardiac apex. There was also a soft diastolic murmur at the aortic area. Small amounts of fluid were noted at the bases of the lungs, but no râles were heard over this area. The liver extended 4 fingerbreadths below the costal margin and pulsated during systole. Ascites and moderate edema of the ankles were present. The vital capacity was 75 per cent of normal. The Wassermann reaction was negative. There were 4,600,000 erythrocytes and the hemoglobin content was 65 per cent (Sahli). Urinalysis revealed no abnormality except 1+ albumin and occasional casts.

The cardiac output as determined by the direct method was 1.79 liters per square meter, or 3.02 liters per minute. The output by the acetylene method was 1.31 liters per square meter, or 2.19 liters per minute.

CASE 2.—*Rheumatic heart disease, mitral stenosis and insufficiency and subacute bacterial endocarditis.*

B. H., a 42 year old woman, was admitted to the medical service complaining of weakness, shortness of breath and "rheumatism." She had chorea when 9 and 13 years old and migratory polyarthritis six months before admission to the hospital. Recently she had been troubled with chills, fever and shortness of breath. The temperature was 101 F., the pulse rate 90 and the blood pressure 100 systolic and 90 diastolic. Petechiae were scattered over the neck. The heart was enlarged

Data for Six Patients

Case No.	Initials	Sex	Age	Etiology of Heart Disease	Cardiac Rate	Rhythm	Diameter of Heart, Cm.	Diameter of Chest, Cm.	Degree of Congestive Failure	Arterial Blood Pressure Mm. of Mercury	Venous Pressure, Cm. of Water	Vital Capacity, % of Normal	Circulation Time (Decholin), Seconds	Metabolic Rate, %	Cardiac Output, Direct Method (Fick)		Stroke Volume (Fick), Cc.	Cardiac Output 3-Sample Acetylene Method (Grollman)		
															Liters per Sq.M.	Liters per Min.		Liters per Sq.M.	Liters per Min.	Oxygen Capacity, Vol. %
1	H. D.	M	56	Rheumatic heart disease	77	Auricular fibrillation	19	31	++	100/84	8.5+	74	35.0	+10	1.79	3.02	39	1.31	2.19	22.3
2	B. H.	F	42	Subacute bacterial endocarditis; rheumatic heart disease	92	Sinus	17	27	0	100/78	6.1+	35	12.5	+26	2.45	3.60	39	1.91	2.81	13.4
3	M. B.	F	75	Arteriosclerosis; hypertensive heart disease	60	Nodal	19	26	++++	190/100	20.0+	40	43.5	+19	2.27	3.77	63	1.69	2.82	20.4
4	W. P.	M	49	Hypertension	106	Sinus	20	32	+	165/130	.....	60	....	+11	2.04	3.63	34	2.06	3.57	....
5	L. A.	M	46	Syphilitic heart disease	74	Sinus	27	30	++	150/68	8.8	53	32.0	+11	1.56	2.50	34	1.65	2.64	15.7
6	M. T.	F	27	Tuberculous pericarditis; dilatation; hypertrophy	88	Sinus	18	29	++	110/74	20.0+	40	17.0	+21	2.04	2.69	31	1.28	1.62	....

in all directions, measuring 17 cm. in its maximum diameter; the thoracic width was 27 cm. At the apex there was a presystolic thrill, the first sound was snapping and there was a rumbling diastolic murmur with presystolic accentuation. The lungs were clear. The fingers and toes were slightly clubbed. The spleen was palpable. There were 3,600,000 erythrocytes, and the hemoglobin value was 53 per cent. Urinalysis showed 1+ albumin and a few red blood cells on several occasions. Culture of the blood showed Streptococcus viridans.

By the direct method the cardiac output was found to be 2.45 liters per square meter of body surface, or 3.6 liters per minute. By the acetylene method the cardiac output was 1.91 liters per square meter of body surface, or 2.81 liters per minute.

CASE 3.—*Generalized arteriosclerosis, hypertension, cardiac hypertrophy and dilatation and possibly cor pulmonale.*

M. B., a 75 year old woman, was admitted to the hospital with the complaint of "high blood pressure," effort dyspnea, paroxymal nocturnal dyspnea and palpitation of the heart. Examination showed the patient to be orthopneic. The lips and nail beds were markedly cyanotic. The blood pressure was 190 systolic and 90 diastolic. The pulse rate was 60, and the beat was regular but with definite pulsus alternans. (The electrocardiogram showed nodal rhythm of type II, with a "coronary" T wave in lead I.) The heart was greatly enlarged, as proved by the teleoroentgenogram. The right ventricle and conus pulmonalis showed definite enlargement. At the apex a gallop rhythm and a systolic murmur were heard. At the bases of the lungs there were numerous râles. Moderate ascites and pitting edema of the legs and skin extending to the twelfth dorsal spine were noted. The peripheral arteries were tortuous and sclerotic. The Wassermann reaction was negative. Urinalysis showed a specific gravity of 1.015 and a trace of albumin. There were 4,400,000 erythrocytes, and the hemoglobin value was 80 per cent (Sahli).

The cardiac output was 3.77 liters per minute by the direct method, or 2.27 liters per square meter of body surface. By the acetylene method the cardiac output was 2.82 liters per minute, or 1.69 liters per square meter of body surface.[18]

CASE 4.—*Arteriosclerotic heart disease, with hypertension and myocardial insufficiency.*

W. P., a salesman aged 49, had symptoms beginning seven months before his admission to the hospital with effort dyspnea. For two weeks he had had attacks of paroxysmal nocturnal dyspnea and slight edema of the ankles. Five years previously he was told that his blood pressure was "high." At the time of the present examination he was neither dyspneic nor cyanotic. The blood pressure was 150 systolic and 120 diastolic. The heart was 20 cm. in diameter, as measured by a teleoroentgenogram. The rhythm was regular. A presystolic gallop rhythm and a systolic murmur were heard at the cardiac apex. The physical signs of fluid in the right side of the thorax were present, and these findings were corroborated by roentgenograms of the chest. Slight pitting edema over the sacrum and moderate edema of both ankles were noted. An electrocardiogram showed inverted T waves in lead I and iso-electric T waves in lead III. There were 4.100,000 erythrocytes, and the hemoglobin value was 78 per cent (Sahli). Urinalysis showed a trace of albumin.

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18. Since the completion of these studies this patient has returned to the hospital in profound congestive failure, with anasarca, deep cyanosis and pulmonary edema. However, the cardiac output by the acetylene method was 2.6 liters per minute twenty-four hours before death.

The cardiac output was 2.04 liters per square meter, or 3.63 liters per minute, by the direct method. The acetylene method showed an output of 2.06 liters per square meter of body surface, or 3.57 liters per minute. Five months later, when the patient was symptom free, the cardiac output by the acetylene method was 3.62 liters per minute.

CASE 5.—*Syphilitic aortitis, aortic insufficiency and myocardial insufficiency.*

L. A., a Negro aged 46, had had a primary syphilitic lesion twenty-four years before admission to the hospital. He complained of shortness of breath and precordial pain. Effort dypsnea as well as paroxysmal nocturnal dyspnea had been present for two years. Recently edema of the ankles and precordial pain had forced him to bed. When studied by us the pulse rate was 100, regular and Corrigan in character. The blood pressure was 155 systolic and 60 diastolic. The heart was greatly enlarged, measuring 27 cm. To and fro murmurs characteristic of aortic insufficiency were heard at the base of the heart. The lungs were clear. The abdomen showed no abnormalities. There was slight edema of the ankles. The Kahn reaction was 3+. There were 5,000,000 erythrocytes, and the hemoglobin value was 90 per cent (Sahli). The urine contained 3+ albumin and a few leukocytes but no casts.

By the direct method the cardiac output was 1.56 liters per square meter of body surface, or 2.5 liters per minute. The acetylene method gave a value of 1.65 liters per square meter, or 2.64 liters per minute. Five months later, when the patient's condition was definitely improved clinically, the cardiac output was 3.25 liters per minute by the acetylene method.

CASE 6.—*Tuberculous polyserositis, cardiac hypertrophy (slight) and dilatation (marked) and cirrhosis of the liver.*

M. T., a woman aged 27, had been engaged in housework. On April 1935 she became short of breath and noticed irregularity of the heart, which she thought followed a "cold" in February. She had a history of syphilis, with a positive Wassermann reaction and had received antisyphilitic treatment during the year preceding her entry into the hospital. She complained of "gas on the stomach" and nausea.

Physical examination showed enlargement of the heart, with a "roaring" systolic murmur at the apex. The blood pressure was 120 systolic and 80 diastolic. Ascites and enlargement of the liver and spleen were likewise noted. The legs were moderately edematous. The diagnosis of rheumatic heart disease was made.

After digitalization and the use of mercurial diuretic and paracentesis of the abdomen and chest the patient was discharged. Subsequently she was repeatedly readmitted for thoracic and abdominal paracentesis. On several occasions bloody fluid was obtained. Injection of this fluid into guinea-pigs did not cause the development of tuberculosis. On several of the various admissions to the hospital the patient had fever. A diastolic murmur at the apex of the heart and systolic pulsations in the jugular veins were noted. Transient auricular fibrillation was demonstrated by the electrocardiogram. A roentgenogram showed cardiac enlargement. The fluoroscopic diagnosis was rheumatic heart disease or pericarditis. There were 4,300,000 erythrocytes, and the hemoglobin value was 60 per cent. The Kahn reaction was negative.

The cardiac output by the direct method was 2.04 liters per square meter, or 2.69 liters per minute. By the acetylene method the cardiac output was 1.28 liters per square meter of body surface, or 1.62 liters per minute.

The patient died six months later after repeated readmissions to the hospital, and at autopsy tuberculous polyserositis was noted. The heart was slightly hyper-

trophied, weighing 400 Gm. It was moderately dilated, with an organized mural thrombus of the left auricle. The cardiac valves were normal. The pericardium was thickened, and the visceral and parietal layers were bound together by fibrinous adhesions. There were no important external adhesions save those to the pleurae.

CONCLUSIONS

As shown in the protocols and table, a close qualitative comparison between the acetylene and the direct method was demonstrated. The results in two patients (cases 4 and 5) were nearly identical. In the other patients, although the acetylene method gave lower values than did the direct method, the relationship was consistent, in that a low output, as measured by the acetylene method, was likewise low with the direct method. This close relative parallelism was shown in every instance and serves to demonstrate the value of the modified acetylene method in the study of patients with serious heart disease.

No correlation between the level of cardiac output and the degree of circulatory inefficiency, as measured by the velocity of blood flow, the venous pressure or the vital capacity, was observed. In other words, one cannot say that the lower the cardiac output, the sicker the patient. In fact, the patient (case 3) who had the largest cardiac output of any of the patients studied unquestionably presented the severest manifestations of congestive failure. This result lends weight to the contention of Harrison that no consistent relationship exists between the degree of failure and the cardiac output. Additional support for this belief is afforded by the measurement of the cardiac output of a patient with complete heart block who exhibited neither symptoms nor signs of cardiac failure and who was studied by Baumann and Lauter [12] with the direct method. The cardiac output was only 2.7 liters per minute, a value lower than those for two of three patients suffering with cardiac asthma who were examined by the same investigator. However, the necessarily small group of patients examined suggests that patients with severe myocardial disease have a subnormal cardiac output even though congestive failure may not be present. In none of the patients was the output as great as normal, either with the acetylene or the direct method. In fact, the output as measured by the direct method gave an average value of 30 per cent below the average normal of 4.6 liters per minute, as reported by Baumann.[13] Unfortunately this investigator failed to express the cardiac output in terms of liters per square meter of body surface, which undoubtedly would have afforded a superior basis for comparison.

SUMMARY

The cardiac output has been determined by the direct method of Fick and the modified acetylene method of Grollman for six patients

with serious heart disease. In all the patients the cardiac output was subnormal.

The results demonstrated close qualitative comparison between the modified acetylene and the direct method, although the absolute values tended to be lower by the acetylene method.

No relationship between the severity of symptoms or the severity of failure, as judged by measurements of circulatory efficiency, and the level of cardiac output was demonstrated.

SUBACUTE COR PULMONALE

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At present two types of cor pulmonale are recognized—acute and chronic. The former is practically always the result of a single cause, pulmonary embolism; for a clearer understanding of its clinical manifestation one is indebted to the recent writings of Sylvester McGinn and Paul D. White.[1] In this form, except in those relatively rare instances in which the patient survives repeated attacks over a long period (two months or longer), there is rarely significant hypertrophy of the right ventricle, since the condition either is rapidly fatal or quickly results in complete recovery.

The chronic type of cor pulmonale is of manifold etiology. The most important causes of primary chronic cor pulmonale are mitral stenosis, extensive pulmonary fibrosis and marked emphysema secondary to asthma, chronic bronchitis or some other pulmonary disease. In 14 per cent of a series of one hundred patients with heart failure White[2] noted primary strain of the right side of the heart due to the aforementioned causes. However, in most of the 74 per cent of the patients in whom there was primary strain of the left ventricle the right chamber was secondarily involved. More recently Thompson and White[3] confirmed White's previous observations by a study of seven hundred and four patients with hypertrophy of the right ventricle. In 61 per cent the strain of the right side of the heart was apparently secondary to failure of the left ventricle, since the causes of cardiac strain in this group were arterial hypertension, aortic valvular disease and infarcts of the left ventricle, with no factors demonstrable which might produce primary strain of the right ventricle.

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Relatively less frequent causes of chronic cor pulmonale are marked deformity of the chest (kyphoscoliosis), certain congenital cardiac lesions, namely, defects of the pulmonary valve, patent ductus arteriosus and septal defects, and rarely organic tricuspid regurgitation.

Chronic infiltrative pulmonary lesions (neoplasms, tuberculosis and other chronic inflammatory processes) involving large portions of the pulmonary tissues often cause strain of the right side of the heart, but in these instances (except when extensive fibrosis or marked emphysema develops) the primary disease usually dominates the clinical picture and causes death before the more serious symptoms of strain of the right side of the heart become apparent.

Pulmonary arteriosclerosis is commonly associated with sustained increased tension in the pulmonary circulation, and the pulmonary vascular changes and the strain of the right side of the heart are usually the simultaneous results of common etiologic factors. According to Moschcowitz,[4] "primary arteriosclerosis of the pulmonary vessels, if it exists at all, is extremely rare." However, instances of extensive pulmonary arteriosclerosis without demonstrable causative factors have been reported by Atkins,[5] Darley and Doan,[6] Pund and Phinizy,[7] Ulrich,[8] Brenner,[9] Krutzsch [10] and others. For many of these patients there was a history or evidence of pulmonary infection (such as tuberculosis, pneumonia or syphilis) sometime prior to the onset of the symptoms of pulmonary arteriosclerosis. Although in most instances the infection had cleared up without significant residua (as determined by clinical and roentgenographic examination or at necropsy), it is possible that during the active stage of the infection sufficient damage had resulted to pulmonary vessels to initiate a sclerosing process which gradually produced narrowing of the pulmonary vascular bed. Congenital anomalies and faulty development have also been suggested as possible

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10. Krutzsch, Günther: Ueber rechtsseitige Herzhypertrophie durch Einengung des Gesamtquerschnittes der kleineren und kleinsten Lungenarterien, Frankfurt. Ztschr. f. Path. **23**:247-271, 1920.

etiologic factors.[7] It is clear, therefore, that in the light of present knowledge the possibility must be recognized that "primary" pulmonary arteriosclerosis (degenerative, toxic, infectious or developmental) may be the cause of pulmonary hypertension, with consequent strain of the right side of the heart. The term "primary" is used here not in the sense of "essential" but to denote that the vascular changes preceded the hypertrophy of the right ventricle and may therefore be considered the probable cause of the hypertrophy.

Ayerza's disease is probably best regarded as a syndrome including pulmonary hypertension, pulmonary arteriosclerosis, polycythemia, cyanosis, headache, mental confusion and somnolence, hemoptysis, strain of the right side of the heart and, in the latter stages, the symptoms of failure of the right side of the heart, with congestion. Often bronchitis and cough precede by months or years the onset of the other symptoms and may therefore be of etiologic significance. Syphilis has been claimed as the cause of Ayerza's disease (Arrillaga,[11] Escudero[12] and Rogers[13]). Although syphilis was found in about half the patients reported on, "in only one of these was there acceptable evidence that the pulmonary arterial lesions were due to syphilis" (Brenner[9]); and since many instances of typical involvement have been reported in which syphilis was definitely excluded (Atkins,[5] Brenner[9] and Hare and Ross[14]), the concept that the Ayerza symptom complex is a specific disease of syphilitic origin must be abandoned. This syndrome probably may develop from any lesion that causes hypertension and arteriosclerosis of the pulmonary circulation (Moschcowitz,[4] Atkins,[5] Waring and Yegge[15] and others). They are essentially the same factors already described (including syphilitic pulmonary disease), and their relationship to strain of the right side of the heart has already been discussed.

Recently Yater and Hansmann[16] suggested sickle cell anemia as "a new cause of cor pulmonale" and reported on two patients in illustration. In both patients hypertrophy and failure of the right side of the heart

11. Arrillaga, F. C.: Sclérose de l'artère pulmonaire, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:292, 1924; cited by Brenner.[9]

12. Escudero, P.: Les cardiaques noirs et la maladie de Ayerza, Arch. d. mal. du cœur **19**:439, 1926; cited by Brenner.[9]

13. Rogers, L.: Extensive Atheroma and Dilatation of the Pulmonary Arteries, Without Marked Valvular Lesions, as a Not Very Rare Cause of Fatal Cardiac Disease in Bengal, Quart. J. Med. **2**:1-17 (Oct.) 1908.

14. Hare, D. C., and Ross, J. M.: Syphilitic Disease of the Pulmonary Arteries, Lancet **2**:808-812 (Oct. 19) 1929.

15. Waring, J. J., and Yegge, W. B.: Polycythemia in Association with Pulmonary Disorders, Ann. Int. Med. **7**:190-207 (Aug.) 1933.

16. Yater, W. M., and Hansmann, G. H.: Sickle-Cell Anemia: A New Cause of Cor Pulmonale, Am. J. M. Sc. **191**:474-484 (April) 1936.

were present. The lesions in one patient were thrombotic occlusions of the small and medium-sized arteries of the lungs; in the other there was thickening of the walls of the small and medium-sized arteries and arterioles of the lungs, with narrowing of their lumens, but thromboses were not observed in the tissue studied. The authors suggested that "right heart failure must be common in cases of sickle cell anemia, since many of the patients have enlarged hearts, systolic murmurs, and hepatomegaly."

It is our purpose in this paper to call attention to a clinicopathologic condition producing "subacute" cor pulmonale. This condition, although admittedly rare, is possessed of sufficiently distinguishing features to suggest the possibility of clinical recognition.

REPORT OF A CASE

A married woman aged 36 entered St Vincent's Hospital because of anemia and uterine bleeding. The only significant statement in her previous history was in reference to some vague gastro-intestinal discomfort of about one year's duration, which she desired to have investigated after the anemia and bleeding were controlled. Otherwise her personal and family records were essentially irrelevant. A diagnosis of uterine myofibromas and secondary anemia was made, and after the giving of a blood transfusion supravaginal hysterectomy was performed. The postoperative course was complicated by the development of a pelvic abscess, which was responsible for the temperature ranging from 100 to 103 F. However, except on three days the temperature remained below 101 F., and it appears fair to state that the pelvic infection was a relatively unimportant factor in the production of the major symptoms and in the final outcome. About one week after the operation the patient complained of cough and difficulty in breathing. These symptoms became increasingly pronounced and failed to respond to any of the usual therapeutic measures. Prior to that there had been nothing in the history or examination to suggest any abnormality of the cardiovascular or respiratory systems.

One week after the appearance of dyspnea and cough (fourteenth postoperative day) the condition of the patient became suddenly alarming. The pulse rate, which had been about 100 per minute, increased to 120 per minute. The respirations, which had been about 30 per minute, mounted to 40 per minute, and the temperature dropped to 97 F. The heart action appeared "toxic," the pulse was weak and the blood pressure was 90 systolic and 60 diastolic. Systolic murmurs were heard over the "right ventricle" (lower portion of the sternum) and at the pulmonic area. There was "a very soft murmur at the aortic area." The lungs appeared clear. The liver was just palpable below the costal margin; the spleen was not enlarged. A roentgenogram showed marked dilatation of the second arch of the left cardiac border (indicating enlargement of the pulmonary artery and conus) and considerable perivascular infiltration, which radiated from both hilar areas into the pulmonary fields. There was evidence of some passive congestion. The blood showed moderate anemia (hemoglobin, 70 per cent; red blood cells, 3,480,000).

These symptoms continued for about forty-eight hours. Gradually the pulse grew weaker and finally became imperceptible. Breathing continued for several minutes after the heart had completely stopped. Cyanosis was not marked until shortly before death.

Clinical Diagnosis.—Before the information obtained at necropsy was available it was recognized that this was a "cardiac" death in which the inadequacy of the right side of the heart played a prominent part. However, neither the nature of this inadequacy nor its pathogenesis was understood. Because of the fever and "murmurs," the presence of endocarditis was suspected at one time but was not regarded as very probable, There was no history of rheumatism or any other condition that might produce heart disease; and physical examination when the patient was admitted to the hospital revealed no evidence of cardiac or pulmonary involvement. The sudden appearance of dyspnea and cough, together with the

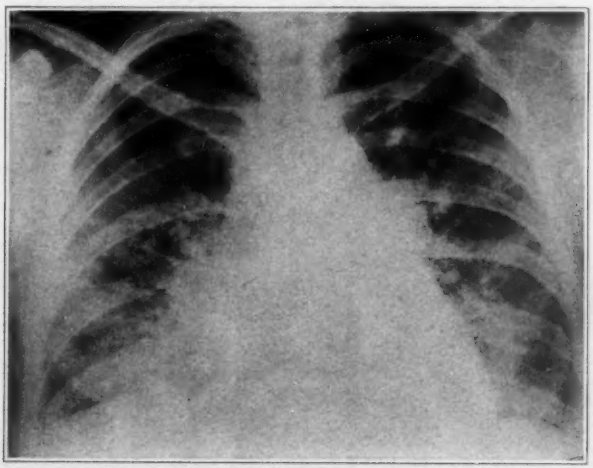

Fig. 1—Roentgenogram taken forty-eight hours before death, showing marked dilatation of the pulmonary artery and conus.

discovery of roentgenographic evidence of strain of the right side of the heart (dilatation of the pulmonary conus), might have suggested the possibility of pulmonary embolism. However, the absence of pain in the chest, hemoptysis and signs of consolidation would have spoken against this diagnosis. The symptoms of shock were also absent at the onset of the cough and dyspnea, although they did develop one week later and persisted during the last two days of life.

Gross Postmortem Examination.—Autopsy was limited to an abdominal incision. The body was that of a well developed and well nourished but rather pale woman. A surgical incision was present in the lower middle portion of the abdomen. It was healing and showed no gross evidence of infection. There was no edema of the extremities or genitalia. A pelvic abscess, located over the cervical stump, contained only a few cubic centimeters of pus. A loop of small intestine was adherent to this site. No free fluid or exudate was present in the abdominal cavity.

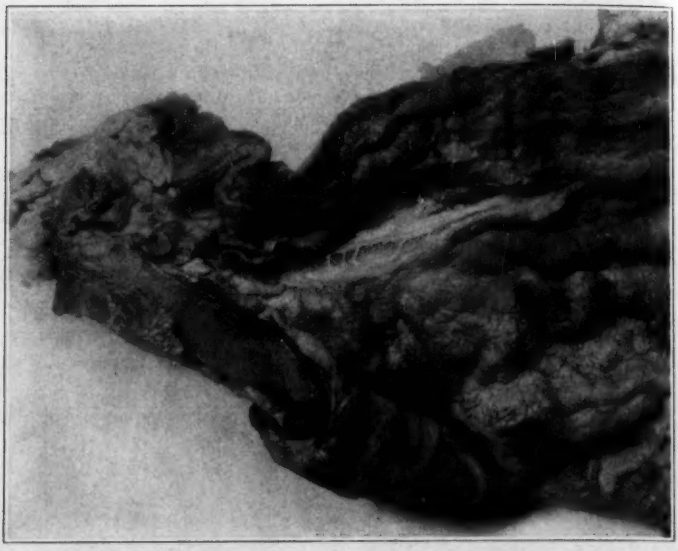

Fig. 2.—Photograph showing the carcinomatous ulcer of the stomach cut through longitudinally. Note the fibrous streaking of the wall associated with the desmoplastic carcinoma.

Fig. 3.—Photograph showing enlargement of the trabeculae carneae and papillary muscles and thickening of the wall of the right ventricle.

The liver weighed 1,420 Gm. and exhibited a smooth capsule with a sharp inferior edge. The surfaces made by sectioning were rather pale, and the parenchyma was friable.

The external aspect of the stomach was unchanged. When the organ was opened, however, the mucosa was seen to be thickened and presented a morocco leather-like roughening on its surface. It was rugose, except for an area, measuring 2.5 by 1.5 cm., in the lesser curvature, near the pylorus, where the

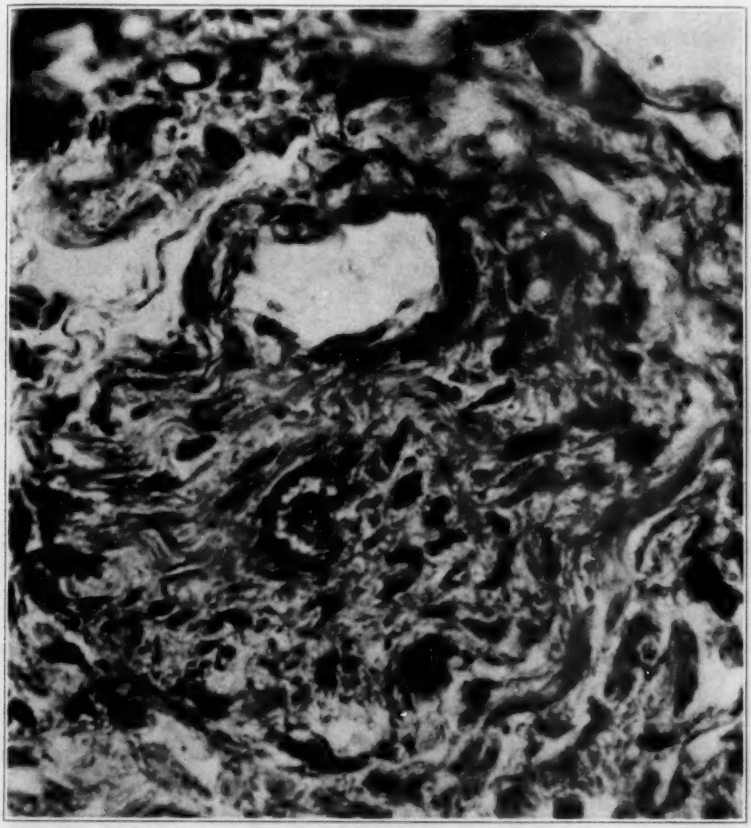

Fig. 4.—High power photomicrograph from a section of the lung, showing a blood vessel with a markedly narrowed eccentric lumen and a hyperchromatic carcinoma cell nucleus at the center of the thickened fibrous intima.

mucosa was firmly fixed to the underlying muscularis. This area was smooth and thin. The underlying serosa and the submucosa were thickened and fibrous, and fibrous strands were seen to extend through the muscularis. Several of the biliary lymph nodes were enlarged; they were firm and discrete and appeared cellular.

The thoracic organs were removed through the diaphragm. The right lung weighed 520 Gm., and the left, 460 Gm. Each exhibited moderate coal-dust mottling but no other gross changes. There was no gross evidence of metastatic carcinoma within the lungs. The tracheobronchial lymph nodes, however, were enlarged gray-black cellular structures and were obviously carcinomatous. The larger branches of the pulmonary artery were unchanged. The pericardial sac contained only a few cubic centimeters of free fluid and presented a smooth, gray inner surface. The heart weighed 340 Gm. The right ventricle was somewhat dilated, with the trabeculae carneae and papillary muscles somewhat enlarged. The myocardium of the right ventricle was 0.5 cm. thick adjacent to the pulmonic ring and 0.8 cm. thick distally. The valvular rings of the heart measured as follows: pulmonic, 8 cm.; tricuspid, 13 cm.; mitral, 9 cm., and aortic, 5.5 cm.

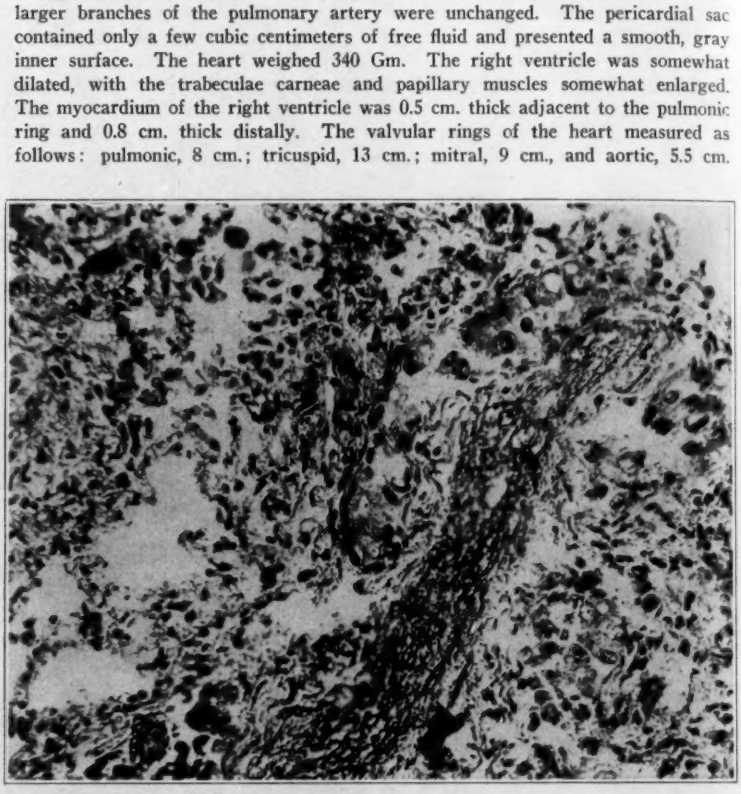

Fig. 5.—Photomicrograph of a section of the lung, showing a longitudinally cut blood vessel filled with fresh thrombus. The vessel is surrounded and somewhat compressed by lymphatic channels filled with metastatic carcinoma cells.

The coronary arteries were unchanged. The myocardium was firm and pale. The left chambers of the heart were unaltered. The conus arteriosus appeared to bulge somewhat anteriorly, without essentially altering the configuration of the heart.

Microscopic Postmortem Examination.—Sections of the lungs showed many distinct carcinoma cells scattered throughout the perivascular and peribronchial lymphatic vessels. These carcinoma cells were polyhedral, with ovoid to spherical hyperchromatic nuclei. They showed no tendency to form glands, and little invasion of the pulmonary parenchyma was noted. The only evidence of actual invasion of the walls of the blood vessels was a single observation of a hyper-

chromatic carcinoma cell nucleus in the thickened fibrous intima of a small blood vessel (fig. 4). Many of the blood vessels were obliterated by recent thrombi composed of strands of fibrin and evenly dispersed erythrocytes. These thrombi were in blood vessels which were adjacent to, and which often appeared to be compressed by, lymphatic vessels abundantly filled with carcinoma cells (fig. 5). In a few of the larger, yet microscopic, blood vessels mural thrombi were seen. No carconima cells were identified in these thrombi, nor were any carcinoma cells seen invading the walls of the blood vessels in contact with these thrombi. Many of the smaller arteries showed marked narrowing of the lumen, because of increased connective tissue of the intima. Connective tissue in various stages of proliferation was seen, ranging from young fibroblasts to well developed

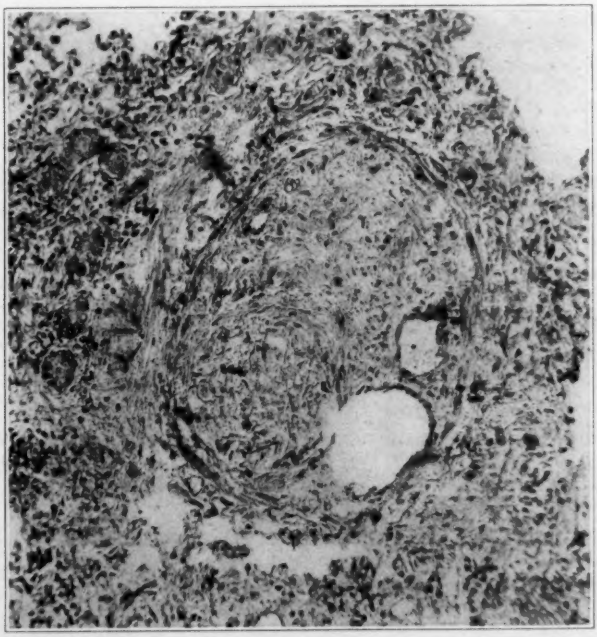

Fig. 6.—Photomicrograph of a small pulmonary blood vessel, showing an organized and canalized thrombus. One channel occupying the left lower quadrant displays secondary occlusion, with more recent organization of the clot than is observed elsewhere. Note the nests of carcinoma cells in the adjacent lymphatic ducts.

collagen-containing strands. This thickening of the intima resulted in varying degrees of narrowing of the vessels, and in some instances complete obliteration of the lumen had occurred. Multiple channels of various sizes were seen to pass through this connective tissue, denoting recanalization of obstructed vessels. A few of these newly formed channels were observed in turn to be occluded by secondary thrombosis and organization (fig. 6). Some connective tissue was also observed in the adventitial region of the blood vessels.

Sections of the stomach taken from the "smooth area" in the lesser curvature near the pylorus showed this area to be the seat of a carcinoma. Carcinoma cells were best seen on the mucosal surface. Here they were polyhedral and contained ovoid to spherical hyperchromatic nuclei. More deeply, spherical and polyhedral epithelial cells, occurring singly or in nests, were seen to invade the tunica propria. Mitotic figures were not numerous. There was some tendency to form small atypical glands, which were seen invading the submucosa and muscularis. This occurred especially in areas where there was an abundance of dense connective tissue containing collagen. The serosa was thickened by the presence of dense connective tissue, and in one section a dilated lymphatic vessel containing many carcinoma cells was noted. These cells were identical with those seen in the lymphatic vessels of the lung.

Sections of the heart showed slight enlargement of the muscle cells of the wall of the right ventricle. No changes were seen in the myocardial cells of the left ventricle.

COMMENT

This case is unique in that death was not due to massive carcinomatous metastases or to toxemia from the growth but resulted from circulatory failure due to obstruction of the pulmonary circulation beyond the point compatible with life. This obstruction was caused by extensive carcinomatous metastasis into the perivascular lymphatic vessels, which in turn produced arteriolar thrombosis, with organization and connective tissue proliferation. The changes in the arterioles appeared to be the results of three factors: (1) the mechanical factor of pressure from the adjacent cancer-filled lymphatic vessels, (2) an active invasion of the walls of the blood vessels by cancer cells and (3) the biologic factor of connective tissue proliferation stimulated by the presence of the desmoplastic tumor in the neighboring lymphatic vessels.

A fairly comprehensive search of the literature yielded only two comparable instances. One was reported by Schmidt [17] 1903 as follows:

A man aged 37 years complained of slight gastric distress for several weeks; otherwise there were complete well-being and an excellent nutritional state. Death occurred suddenly. Autopsy revealed dilatation and some hypertrophy of the right ventricle, especially of the pulmonary cone. The lungs showed grossly numerous fine, white, ramified cordlike threads passing through all lobes of both lungs, corresponding to the distribution of the vessels. Nothing like this was noted in the pleurae. There were no tumors, nodules in the pulmonary tissue or cancerous deposits under the mucosa of the bronchi. Microscopically the small arteries in the lungs with a diameter of 0.75 mm. or less were filled with thrombi of different structure. This has occurred so evenly and so extensively that in many sections hardly a single vessel of this caliber was unchanged. The lumen contained partly fibrinous, partly hyaline, granular thrombi and epithelial cells, which formed accumulations of a mosaic-like order and which when compared with the cells of the stomach and those of the lymph nodes were undoubtedly

17. Schmidt, M. B.: Die Verbreitungswege der Karzinome und die Beziehung generalisierter Sarkome zu den leukämischen Neubildungen, Jena, Gustav Fischer. 1903.

cancer cells. Nowhere in the carefully examined lungs could cancer cells be seen except in the lumen of the blood vessels. None were seen in the perivascular lymphatic vessels, the pulmonary tissue or the walls of the blood vessels.

In the stomach was noted a circular, infiltrating, almost completely ulcerated scirrhous carcinoma 1 to 2 cm. above the end of the pyloric ring.

The postmortem diagnosis was carcinoma of the stomach, and the cause of death was regarded by the author as being related to the hypertrophy of the right side of the heart, which resulted from obstruction of the arterial circuit within the lungs by old organized thrombi. The sudden death was possibly due to the new import of cancerous material. Clinically, however, the presence of a cancerous lesion was not suspected, and no explanation could be given (ante mortem) for the enlargement of the right side of the heart.

The other patient was reported on by Krutzsch [10] (1920) as follows:

A 40 year old city clerk was admitted on Aug. 27, 1917, to the city hospital of Dresden-Friedrichstadt. At the age of 17 the patient had a purulent infection of the right leg and the upper portion of the left arm. After an operation the condition was recognized as being of syphilitic origin and was cured with mercurial inunctions and potassium iodide. One year previously symptoms suggestive of peptic ulcer appeared. For two months increasing tiredness, weakness and palpitation had been noted, and during the last three weeks the patient appeared pale.

Examination.—The patient was of medium size and in a reduced state of nutrition and strength. The lips and nails were strongly cyanotic. Examination of the lungs revealed normal sounds; there were few bronchitic sounds. The heart was slightly broader toward the right, with impure tones. The pulse was small and rapid. The abdomen was soft, and the gastric region showed tenderness but no definite resistance. The liver was somewhat firm but not enlarged. The nervous system was normal. Examination of the urine revealed a trace of albumin but no sediment. The Wassermann reaction was negative.

Treatment.—Caffeine, morphine and codeine were administered.

Course.—There was an increasing decline, with frequent vomiting. The hemoglobin value was 65 per cent. A blood smear showed poikilocytosis and a normal proportion of leukocytes. Death occurred on August 31, four days after the patient's admission to the hospital.

The author stated that as for Schmidt's patient, the clinical history offered no explanation of the increase of the size of the right side of the heart. The clinical diagnosis was severe anemia, chronic gastric ulcer and endocarditis.

Postmortem Examination.—The heart was slightly larger than the fist. The right chamber was 10 cm. long and somewhat dilated; the musculature was 8 mm. thick and imparted a feeling of stiffness; the papillary muscles and trabeculae were prominent. The left chamber was 9 cm. long, and its wall was 12 mm. thick.

The lungs were large and contained air. The pulmonary tissue was a little denser than normal. The surface showed extraordinarily numerous fine grayish white linear markings in reticular order, which corresponded to the generally bluish lymphatic vessels in the visceral pleura. The pleura was smooth and shiny. The fine white linear markings stood out somewhat from the surface. Sectioned tissue was grayish red. Extraordinarily numerous white lines, about 0.25 to 0.5 mm. wide, were prominent and corresponded to the borders of the lobules. Grossly no changes were evident in the blood vessels of the lung. Microscopically, practically all the smaller arteries of the lung (at least three fourths of them) had become

plugged by thrombi. Some were old, and the plugs were intimately united with the walls. Sections through these thrombi no longer revealed definite evidence of carcinoma cells. In other sections the fibrosis had not progressed so far, and there were still some small but definitely recognizable accumulations of cancer cells visible amid the connective tissue coming from the wall. Occasionally in an old thrombus there were seen newly formed vessels running parallel to the axis of the old vessels. Often in the newly formed vessels were seen carcinomatous emboli, which appeared freshest and most viable because the nuclei were strongly stained. At least as numerous as in the blood vessels were the carcinomatous plugs in the lymphatic vessels of the lungs, where the entire picture gave the impression of a young, strongly proliferative formation. Obliteration with carcinomatous plugs was noted in the peribronchial, perivascular, interalveolar and subpleural lymphatic vessels. In longitudinal sections the completeness of the filling of the lumen was evident. The caliber of the lymph vessels was enlarged. Whenever a network of cancer-filled perivascular lymphatic vessels surrounded a thin-walled artery, the latter was obliterated through pressure exerted on it by these lymphatic vessels. No cancer cells were seen anywhere outside the vascular structures. The pulmonary parenchyma showed evidence of only passive congestion.

The stomach showed a carcinomatous ulcer of the small curvature. The lesion was about 8 cm. in length, and at places 2.5 cm. in thickness.

In conclusion the author remarked that by the obstruction (thrombosis) of the pulmonary circulation the lesser circuit was gravely disturbed. The fully organized thrombi and the long duration of the process were evidently responsible for the hypertrophy of the right side of the heart.

The three patients whose histories have been described showed strikingly similar conditions both clinically and pathologically. Their ages were 36, 37 and 40 years, respectively. They each suffered from gastric distress for about a year. In two instances a diagnosis of peptic ulcer was made. In all three patients, without any previous history of cardiopulmonary disease, there developed rapidly (in a few days or weeks) symptoms of strain of the right side of the heart. For two of the patients either a diagnosis of endocarditis was made or the presence of this condition was suspected. For none was there an adequate explanation (ante mortem) of the strain of the right side of the heart. Pathologically the end-results were identical for all three patients, namely, hypertrophy and dilatation of the right side of the heart due to extensive obstruction of the pulmonary circulation. In Schmidt's patient the obstruction was limited to the arterioles; in Krutzsch's patient the lymphatic vessels and the arterioles were equally affected; in our patient the primary involvement was apparently in the perivascular lymphatic vessels, and the arteriolar obstruction was secondary.

In all three patients the immediate cause of death was failure of the right side of the heart which had developed more or less suddenly after a relatively brief period (of from two weeks to two months) of illness characterized by symptoms of strain of the right side of the heart. It is suggested that this clinical picture is most accurately

described by the term subacute cor pulmonale. It is further suggested that this subacute type of cor pulmonale may be differentiated clinically from either the acute or the chronic type. In the former the onset is explosive, with a great deal of shock, often associated with pain, and is not preceded by any period of insidious symptoms of strain of the right side of the heart. The patient with the chronic type of cor pulmonale generally presents clear evidence of the causative factors for many years; and relatively rarely when clear evidence of the causative factor is absent, the symptoms of strain of the right side of the heart continue for many years or at least for many months before death ensues from failure of the right side of the heart. In the reports of the cases of primary pulmonary arteriosclerosis collected by Brenner [9] the duration of symptoms of strain of the right side of the heart was stated as having been from five months to five years, the average being about two years.

So far as we know no pathologic process other than that presented by the three patients included in this report has ever been noted in association with a clinical picture like the one here described under the term subacute cor pulmonale. If this observation is correct, it is probable that subacute cor pulmonale, as described in this communication, is a distinct clinicopathologic entity which can be recognized clinically. Its chief distinguishing feature is the rapid development of signs and symptoms of strain of the right side of the heart in a patient who gives no history of antecedent cardiopulmonary disease or any other condition known to be capable of producing strain of the right side of the heart. A history of "peptic ulcer" or of vague gastric discomfort over a period of several months or a year offers additional suggestive evidence. However, although in all three patients the primary lesion was in the stomach, the possibility must be admitted that a similar clinicopathologic picture may arise from a carcinoma originating in some other organ. Schmidt [17] observed cancerous metastasis in the pulmonary vessels in fifteen of forty-one patients with carcinoma. In seven of these fifteen patients the primary growth was in the stomach; in the remaining eight the primary growth was in other organs of the abdomen and pelvis. But in only one of the fifteen (the patient whose case is reviewed in the present report) was the involvement of the pulmonary vascular tree sufficiently extensive to produce subacute cor pulmonale.

The type of cardiac failure which occurred in these three patients appears to be comparable to the cardiac failure resulting from graded compression of the pulmonary artery of dogs described recently by Fineberg and Wiggers.[18] These investigators have shown that the right

18. Fineberg, M. H., and Wiggers, C. J.: Compensation and Failure of the Right Ventricle, Am. Heart J. **11**:255-263 (March) 1936.

ventricle is able to compensate compression of the pulmonary artery up to an average of about 58 per cent, and up to that point there is no measurable change in the output of the left ventricle. Under these circumstances the aortic pressure is unchanged, and the systemic circulation remains adequate. During this time the right ventricle gradually hypertrophies and becomes accommodated to the increased load. If the resistance in the pulmonary circulation is increased beyond the point of potential compensation (i. e., more than the 58 per cent of average compression), the right ventricle distends, and the venous pressure rises. A lessened amount of blood is propelled through the pulmonary bed into the systemic circulation, and there is a drop in the aortic pressure. Owing to the fact that a lessened amount of blood becomes available for the coronary circulation, a vicious circle is established which accelerates the failure of the right ventricle. At this stage death may result from congestive failure or from a failure of the pacemakers, in which case the heart stops completely, and death takes place before there is time for marked congestive failure to occur.

It seems probable that the last-mentioned mechanism supervened in the three patients reported on here. There was but slight passive congestion evident at necropsy in all three instances. In two of the patients death was apparently sudden. In our own patient it was noted that during the last hour of life the pulse could not be felt. Finally the heart stopped, while breathing still continued. It is regrettable that electrocardiograms are not available. Much interesting information might have been derived from serial tracings picturing the events in the final hours of life.

The entire record suggests that here nature has duplicated the experiment of "graded compression of the pulmonary artery." The sections from the lungs indicated that at the time of death there was more than 60 per cent obliteration of the pulmonary vascular bed, and yet no symptoms of strain of the right side of the heart appeared until about ten days before death, and alarming symptoms did not become manifest until the last forty-eight hours of life. At necropsy the right ventricle showed relatively mild hypertrophy, although roentgenographic examination two days before death disclosed marked dynamic dilatation of the pulmonary conus.[19] Thompson and White [8] estimated that strain for about two months is necessary to produce appreciable hypertrophy of the right ventricle. The degree of hypertrophy of the right ventricle in our patient and the time of the appearance of symptoms might suggest that the pulmonary vascular invasion by the carcinoma had been in progress for three or four months and that the appearance of

19. Dynamic dilatation of the pulmonary artery and conus that is seen during life may be absent at necropsy. Similar cases have been reported on by J. B. Schwedel and B. S. Epstein (Am. Heart J. **11**:292-302 [March] 1936).

symptoms ten days before death marked the point at which the obliteration of the pulmonary vascular bed reached a degree in excess of the limit to which the right ventricle was able to become adjusted. From this point on the downward progress was rapid, just as was noted in the experiments on animals conducted by Fineberg and Wiggers.[18]

SUMMARY

The record of a patient whose death from failure of the right side of the heart resulted from rapid obstruction of the pulmonary circulation is presented. Both the pulmonary lymphatic vessels and the pulmonary arterioles were involved. The obstruction in the lymphatic vessels was the result of extensive invasion by metastatic carcinoma. The changes in the arterioles consisted of thrombosis with organization, intimal connective tissue proliferation and occasional invasion of the walls of the vessels by carcinoma cells. These changes were interpreted as the result of three factors: (1) pressure effects from the adjacent cancer-laden lymphatic vessels, (2) connective tissue proliferation due to the desmoplastic nature of the growth and (3) direct contact invasion of the walls of the blood vessels. The original tumor arose from the stomach, and its presence remained clinically unsuspected.

Reports of two comparable cases found in the literature are reviewed. These three records are strikingly similar, and it is suggested that they represent a clinicopathologic entity which may best be described by the term subacute cor pulmonale.

Dr. William Shea permitted us to examine the clinical records and make a postmortem examination in this case.

RELATION OF KIDNEYS TO BLOOD PRESSURE

EFFECTS OF EXTRACTS OF KIDNEYS OF NORMAL DOGS AND OF DOGS WITH RENAL HYPERTENSION ON BLOOD PRESSURE OF RATS

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Goldblatt and his co-workers [1] have recently shown that a sustained increase in blood pressure may be produced in dogs by partial occlusion of the renal arteries. This observation has been confirmed by numerous investigators, including Page,[2] Prinzmetal and Friedman [3] and ourselves. Since the hypertension is not relieved by denervation of the kidney, can be produced in animals subjected to previous renal denervation [2] and occurs even when the kidney has been transplanted into the neck,[4] the rise in blood pressure appears to be of "chemical" rather than "nervous" origin.

Hartwich [5] showed that ureteral ligation caused a rise in blood pressure in dogs. Similar results were reported by others,[6] who found that

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From the departments of Medicine, Surgery and Biochemistry, Vanderbilt University.

This study was aided by a grant from the Division of Sciences of the Rockefeller Foundation.

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2. Page, I. H.: The Relationship of the Intrinsic Renal Nerves to the Origin of Experimental Hypertension, Am. J. Physiol. **112**:166, 1935.

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6. Harrison, T. R.; Mason, M. F.; Resnik, H., and Rainey, J.: Changes in Blood Pressure in Relation to Experimental Renal Insufficiency, Tr. A. Am. Physicians **51**:280, 1936.

previous denervation of the kidney did not prevent the effect. It has recently been observed [7] that ureteral ligation may cause a well marked diminution of the blood flow through the kidneys of unanesthetized dogs. Since ischemia of the kidneys should occur both after ureteral ligation and after the partial obstruction of the renal arteries, it seems that this functional change possibly is related in some way to the rise in blood pressure which occurs subsequent to these procedures.

The observations which have been cited on the denervated and transplanted kidney suggest that the rise in blood pressure may be brought about by some substance formed in the ischemic kidneys which reaches the rest of the body through the blood stream. However, attempts made by Page [8] and Prinzmetal and Friedman [3] to demonstrate such a pressor substance in the blood of animals with hypertension due to renal ischemia yielded negative results. In experiments previously reported [9] the problem was approached from a different angle, the pressor effects of extracts of normal and of ischemic kidneys being compared in unanesthetized dogs. It was found as a general rule that the extracts of ischemic kidneys caused a greater rise in blood pressure. Similar results were reported by Prinzmetal and Friedman.[3] However, interpretation of these findings was complicated by the fact that in dogs the renal extracts usually produced an initial decline in blood pressure, collapse occurring frequently and death occasionally. Furthermore, it was found [9] that depressor effects were more frequently encountered after the injection of extracts of normal kidneys than after the injection of extracts of ischemic kidneys. It was therefore uncertain whether the greater rise in blood pressure following the administration of extracts of ischemic kidneys was due to an increased amount of pressor material or to a decreased amount of depressor substance in these as compared with normal kidneys.

Attempts were next made to separate pressor and depressor agents by subjecting the renal extracts to various methods of purification. The attempts were only partially successful. Certain facts were learned concerning the chemical nature of the renal pressor substance,[10] which

7. Levy, S. E.; Mason, M. F.; Harrison, T. R., and Blalock, A.: The Effects of Ureteral Occlusion on the Blood Flow and Oxygen Consumption of the Kidneys of Unanesthetized Dogs, Surgery **1**:238, 1937.

8. Page, I. H.: Vaso-Pressor Action of Extracts of Plasma of Normal Dogs and Dogs with Experimentally Produced Hypertension, Proc. Soc. Exper. Biol. & Med. **35**:112, 1936.

9. Harrison, T. R.; Blalock, A., and Mason, M. F.: Effects on Blood Pressure of Injection of Kidney Extracts of Dogs with Renal Hypertension, Proc. Soc. Exper. Biol. & Med. **35**:38, 1936.

10. Mason, M. F.; Williams, J. R., Jr., and Harrison, T. R.: Observations on Two Different Pressor Substances Obtained from Extracts of Renal Tissue, to be published.

could be freed, in large measure, of depressor agents, but it has not been possible as yet to recover it quantitatively. Therefore, no attempt has been made to compare the pressor properties of purified extracts from normal kidneys and those from ischemic kidneys.

We have recently found that rats anesthetized with pentobarbital sodium display little or no depressor reactions to the injection of renal extract. The use of these animals as test objects has allowed us to compare again the pressor activity of extracts from normal and extracts from ischemic kidneys under conditions which are not complicated by the confusing effects of collapse and other untoward reactions.

In 1898 the pressor property of renal tissue was reported by Tigerstedt and Bergman,[11] who found that saline extracts of the kidneys of rabbits produced a well marked increase in blood pressure when administered intravenously to other rabbits. They named the active principle renin. Shaw [12] confirmed these observations, using cats as test animals. He also found, as had Vincent and Sheen,[13] that the renal extracts often had a marked preliminary depressor action. Shaw emphasized that the results obtained were influenzed by the type and depth of anesthesia. Bingel and Strauss [14] used the autolyzed press juice of kidneys and made similar preparations from most of the other tissues of the body. The juice from the latter usually caused a decline in blood pressure, while that from the kidneys had a pronounced pressor effect. More recently the pressor action of preparations of renal tissue has been confirmed by Thauer [15] and by Hartwich and Hessel.[16] The latter authors made extensive investigations of the properties of renin. Hessel and Maier-Hüser [17] reported that they had been able to purify renin and had obtained it in a powdered form free from histamine and other depressor substances, but they did not give their method of purification. The

11. Tigerstedt, R., and Bergman, P. G.: Niere und Kreislauf, Skandinav. Arch. f. Physiol. **8**:223, 1898.

12. Shaw, H. B.: Autointoxication: Its Relation to Certain Disturbances of Blood Pressure, Lancet **1**:1295 and 1375, 1906.

13. Vincent, S., and Sheen, W.: The Effects of Intravascular Injections of Extracts of Animal Tissues, J. Physiol. **29**:242, 1903.

14. Bingel, A., and Strauss, E.: Ueber die blutdrucksteigernde Substanz der Niere, Deutsches Arch. f. klin. Med. **96**:476, 1909.

15. Thauer, R.: Die Wirkung von Nierenpress-säften und-Extrakten auf den Blutdruck von Versuchstieren, Zentralbl. f. inn. Med. **54**:2, 1933.

16. Hartwich, A., and Hessel, G.: Experimentelle Untersuchungen zur Kreislaufwirkung körpereigener Stoffe, Zentralbl. f. inn. Med. (no. 18 a) **53**:612, 1932. Hessel, G., and Hartwich, A.: Chemische Eigenschaften des blutdrucksteigernden Prinzips in Nierenautolysaten, ibid. **53**:626, 1932.

17. Hessel, G., and Maier-Hüser, H.: Ueber das Renin, einen körpereigenen kreislaufwirksamen Stoff, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **46**:347, 1934.

observations of others[10] were in agreement with those of previous workers in indicating that renin is a protein and suggested that it has certain properties resembling those of the pseudoglobulins.

Several authors investigated the site of action of renin and found that it acted directly on the blood vessels, the pressor effect being observed after decapitation, chordotomy and vagal section. There was a pronounced constrictor action in isolated preparations.

The object of our experiments has been to determine whether or not the pressor substance described by various authors as being present in renal tissue could be demonstrated in greater quantities in the kidneys of animals with experimental renal hypertension.

METHOD

Hypertension was produced in one group of dogs by the application of a Goldblatt clamp to one renal artery, the kidney being explanted to the flank and the opposite kidney being subsequently removed. After a significant rise in blood pressure had occurred, the ischemic kidney was removed under local anesthesia. For purposes of comparison, normal kidneys were taken from healthy dogs killed by bleeding from an arterial cannula inserted while the area was under local anesthesia. Extracts were made also from the normal and abnormal kidneys of dogs in which hypertension had developed as the result of the application of a clamp to one renal artery. The blood pressure of the dogs was measured either by puncture of the femoral artery with a needle or by means of the cuff described by Ferris and Hynes,[18] the passage of the pulse wave being determined by palpation of the dorsal artery of the foot.

The freshly removed kidneys were weighed, chopped into fine particles with scissors, ground in a mortar with carborundum and physiologic solution of sodium chloride, which was added in a ratio of 2 cc. for 1 Gm. of kidney. After thorough grinding, the suspension was centrifugated. The supernatant fluid was kept in the icebox and again centrifugated before injection. Large rats, weighing from 300 to 500 Gm., were anesthetized by the intraperitoneal injection of pentobarbital sodium, the dose being approximately 4 mg. per hundred grams. A needle (16 or 18 gage) was tied into the lower portion of the abdominal aorta, and the mean blood pressure was measured on a mercury manometer. The manometer tubing had such a small bore that a satisfactory float could not be devised. Consequently, no graphic record was made, the blood pressure being read and recorded every fifteen seconds. The manometer was attached to the needle by means of a three way tap, through which injections could be made into the aorta. In order to standardize the procedure, all injections were made at a rate of 1 cc. in fifteen seconds. The amount of renal extract injected varied from 0.25 to 1.5 cc., the usual amount being 1 cc.

Preliminary observations with this technic showed that mechanical effects on the blood pressure due to the increase in the volume of blood usually reached a maximum within a few seconds after the end of the injection, while pressor

18. Ferris, H. W., and Hynes, J. F.: Indirect Blood Pressure Readings in Dogs: Description of Method and Report of Results, J. Lab. & Clin. Med. **16**:597, 1931.

responses to renal extract did not reach a peak for one or more minutes. Consequently, readings obtained during the first thirty seconds after the injection have been discarded. Since slow spontaneous rises in blood pressure sometimes occurred, increases appearing more than five minutes after the injection also have been neglected.

The rises in blood pressure have been computed by comparing the average of the three highest successive readings noted after the administration of renal extract with the average value during the minute prior to the injection.

It was soon found, as previously noted by Bingel and Strauss,[14] that successive injections of the same dose of the same renal extract caused progressively less pressor effect (chart 1), the blood pressure tending to become stabilized at a somewhat higher level after each injection. Consequently, for comparative purposes the response to a given injection has been compared not with the effect

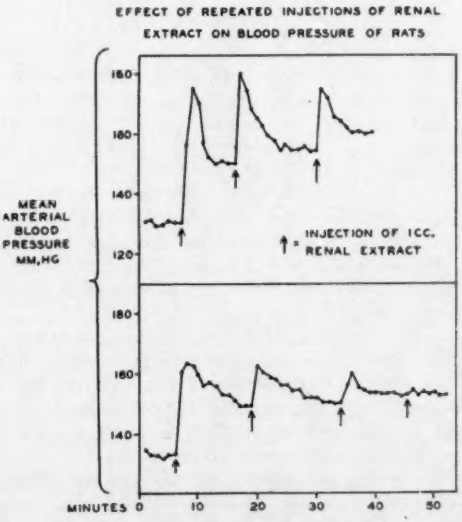

Chart 1.—In each experiment the same extract was injected repeatedly. In both the first injection produced a greater rise in blood pressure than did the second, which caused a more marked response than did the third. After each injection there was a tendency for the blood pressure to become stabilized at a somewhat higher level.

of the preceding or succeeding injection but with the average of the effects of the two injections, the extract of normal and that of ischemic renal tissue being administered alternately.

RESULTS

Forty-seven comparisons were made (nineteen different rats being used) between the pressor effects of ischemic kidneys from six dogs with hypertension and the normal kidneys of five dogs with normal

blood pressure. The data are presented in table 1 and illustrated in chart 2. In two instances the "normal extract" caused a greater rise in blood pressure than did the "ischemic extract." The latter was more pressor in thirty-four instances. Eleven comparisons were regarded as inconclusive, i.e., the differences were less than 5 mm. of mercury.

Thirty-three comparisons were made (fourteen different rats being used) between the pressor effects of the normal and those of the ischemic kidney of the same dog. Twice the "normal extract" gave greater

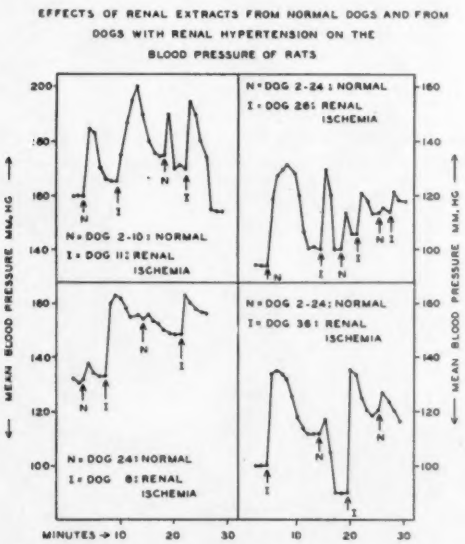
EFFECTS OF RENAL EXTRACTS FROM NORMAL DOGS AND FROM DOGS WITH RENAL HYPERTENSION ON THE BLOOD PRESSURE OF RATS
N = DOG 2-10 : NORMAL
I = DOG 11 : RENAL ISCHEMIA
N = DOG 2-24 : NORMAL
I = DOG 28 : RENAL ISCHEMIA
N = DOG 2-24 : NORMAL
I = DOG 24 : RENAL ISCHEMIA
N = DOG 2-24 : NORMAL
I = DOG 36 : RENAL ISCHEMIA
MEAN BLOOD PRESSURE MM. HG
MINUTES → 10 20 30

Chart 2.—Four comparisons are shown of the pressor effects of extracts of kidneys of normal dogs and of extracts of kidneys of dogs with hypertension due to renal ischemia. In three of the experiments it is obvious that the latter extracts had a more pronounced pressor effect. The results of the fourth comparison (upper right graph) are less definite. This rat became markedly less sensitive as the injections were repeated. When the response to the "ischemic extract" is compared with that of the preceding injection of "normal extract," there is apparently little difference. However, when the effect of the second injection is compared with the average effect of the first and the third, when the effect of the third is compared with the average effect of the second and the fourth and so forth, it is seen that the "ischemic extract" is definitely more effective than the "normal extract."

effects; twenty-two times the "ischemic extract" was more effective; nine comparisons were inconclusive. The data are presented in table 2 and graphically in chart 3.

TABLE 1.—*Effects of Injection of Saline Extracts of Normal and Ischemic Kidneys of Different Dogs on the Arterial Blood Pressure of Rats* *

Rat No.	Rise in Blood Pressure, Mm. Hg †		Dogs from Which Kidneys Were Obtained				
			Normal Kidney		Ischemic Kidney		
	From Normal Kidney	From Ischemic Kidney	Dog No.	Blood Pressure, Mm. Hg	Dog No.	Blood Pressure Before Operation	Blood Pressure When Kidney Was Removed
2-11-3	5 **9** 12	**36** 30 **25**	2-10	Not taken	11	122	180
2-12-5	35 **30**	42 38					
2-12-3	**20** 15	35 **30**					
2-13-1	**6** 0 0 **0**	18 **11** **13** 13					
2-16-4	0	**28**	24	128	6	126	166
2-16-3	11	32					
2-16-2	6 **3** 0	**14** 4 **6**					
2-16-1	**3** 0 **0** 0	30 **21** 10 **5**					
2-22-8	1 **0**	**19** 12	24	128	20	119	162
2-22-6	**4**	11					
2-22-5	11 12	**21** **16**	92‡	154			
2-22-7	8 **5**	**11** 6	24	128	22	124	165
2-22-8	**2** 5	5 **5**					
2-22-5	11	10	92‡	154			
2-22-2	**18** 0	4 **3**	74C (Mange, severe anemia)	134			
2-22-1	25	**16**					
2-24-1	**8** 3	24 **18**	24	128	36	130	186
2-24-2	4 **6**	**40** 45					
2-24-3	0	**25**					
2-24-3	8	**10**	224	118			
2-24-4	13 **7** 0	**13** 13 **10**	74C	134	26	135	173
2-24-4	8	**16**	224	118			
2-24-5	**26** 14 **9** 3	30 **22** 14 **10**					

* Summary:

Ischemic kidney greater than normal kidney (by 5 mm. or more)	34 times
Normal kidney greater than ischemic kidney (by 5 mm. or more)	2 times
Inconclusive (i. e., difference of less than 5 mm.)	11 times
Total number of comparisons	47

† The black figures represent the average effect of two injections, one before and one after the response shown in the opposite column.

‡ This dog has a clamp on the renal artery of the other kidney.

In view of the inherent difficulties in such a method of biologic assay due to differences in the sensitivity of different animals and to spontaneous variations in blood pressure and with allowances made for the pronounced although irregular decreases in responsiveness to repeated injections of the same extract, it seems that the few exceptional results can be neglected as being due to experimental error. We therefore believe that the observations indicate that—so far as can be judged from the test object employed—extracts of ischemic kidneys obtained from dogs with experimental renal hypertension have a more pronounced pressor effect than do extracts of normal kidneys of dogs. The difference is apparently due not to differences in content of depressor substance but to an excess of pressor substances. It should be emphasized, however, that the difference between normal and ischemic kidneys is

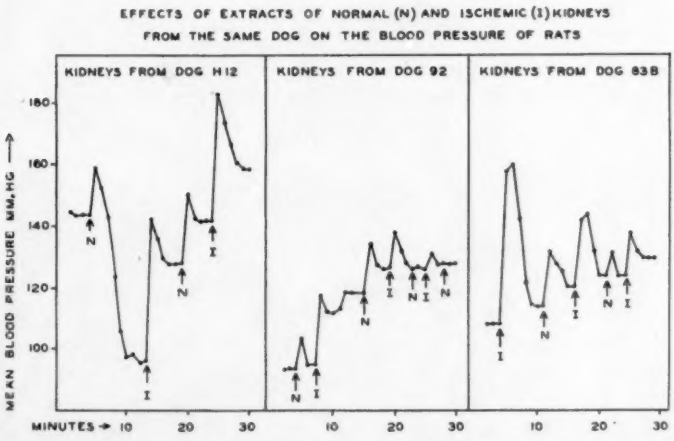

Chart 3.—The kidneys were removed from three dogs each of which had hypertension as the result of partial obstruction of one renal artery. The pressor property of the ischemic kidney was compared with that of the normal kidney of the same dog. In each instance the extract of the ischemic kidney caused a greater rise in blood pressure than did that of the normal kidney.

quantitative rather than qualitative, for all the normal kidneys tested had definite pressor effects when sufficient amounts were injected into sensitive animals.

In order to determine whether ischemia of organs other than the kidney leads to the appearance of increased amounts of pressor substances, the following observations were made: Partial occlusion of one of the main branches of the splenic artery and of the left renal artery of a dog was induced with Goldblatt clamps. A main branch of the

hepatic artery was ligated. Five days later the animal was killed, and saline extracts were made of normal and of ischemic tissue of the spleen, liver and kidney. All these extracts had pressor effects when injected into rats. However, the responses to the extracts of liver and spleen

TABLE 2.—*Effects of Injection of Saline Extracts of Normal and Ischemic Kidney of Same Dog on the Arterial Blood Pressure of Rats* *

	Rise in Blood Pressure, Mm. Hg †		Dog from Which Kidneys Were Obtained		
				Blood Pressure, Mm. Hg	
Rat No.	From Normal Kidney	From Ischemic Kidney	Dog No.	Average Before Operation	When Kidneys Were Removed
2-19-6	13	16	H12	129	172
2-19-5	18	46			
	21	42			
2-19-4	2	4			
	4	10			
2-19-3	5	12			
2-20-1	0	12			
2-22-6	14	22	92	98	158
2-22-4	15	22			
	16	17			
	8	12			
	1	8			
	1	5			
2-22-3	3	7			
	1	6			
2-25-4	18	38	83B	137	154
	13	24			
	8	19			
2-25-3	10	20			
	14	17			
	14	14			
2-25-2	0	23			
2-25-1	12	20			
	15	17			
	28	19			
	30	22			
2-26-1	23	51			
	20	37			
	14	23			
	7	17			
2-26-2	0	23			
	1	15			
	1	14			

* Summary: Ischemic kidney greater than normal kidney (by 5 mm. or more).. 22 times
Normal kidney greater than ischemic kidney (by 5 mm. or more).. 2 times
Inconclusive (i. e., difference of less than 5 mm.)..... 9 times
Total number of comparisons..... 33

† The black figures represent the average effect of two injections, one before and one after the response shown in the opposite column.

were different—being of shorter duration—from the more sustained effects produced by the extracts of the kidneys. Furthermore, the ischemic renal tissue had a more pronounced pressor effect than did the normal renal tissue, but no such differences were observed in the case of the preparations from the other organs (chart 4 *A*). Since it has been shown [10] that pressor effects due to a tyramine-like substance may be obtained from organs other than the kidney, extracts were also pre-

pared by grinding the tissues in alcohol and testing the water-soluble fractions of the alcohol-insoluble portions. (Since tyramine is soluble in alcohol and the specific renal pressor substance is not, this procedure allows one to separate the two principles.) The results (chart 4 *B* and *C*) showed clearly that ischemic liver and ischemic spleen do not contain detectable amounts of the specific renal pressor substance. In the case of the kidney, however, the alcohol precipitates from the ischemic organ were more actively pressor than the same fractions from the normal organ. It therefore appears that the increased pressor effect obtained from ischemic renal tissue is due to an increase in the concentration of the renal pressor substance (Tigerstedt's renin).

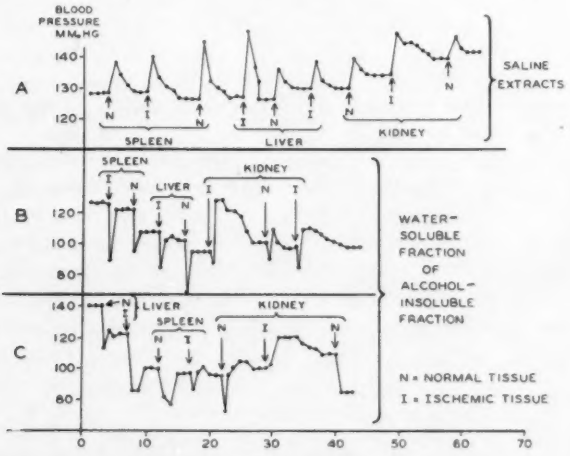

Chart 4.—*A*, pressor effects were obtained from saline extracts of all the tissues. However, in the case of the liver and spleen the extracts of the ischemic tissues showed no greater action than did the preparations from the normal tissue. The duration of the pressor effects was longer with renal extracts, and the usual difference between normal and ischemic kidneys was found. *B* and *C*, when extracts prepared by precipitation with alcohol were tested, only depressor responses were obtained from the liver and spleen. However, the same method of preparation yielded pressor renal extracts, the ischemic kidney being more active than the normal kidney.

COMMENT

The findings which have been reported naturally suggest that the increase in blood pressure produced in animals by experimental renal ischemia is dependent on the excessive formation of a pressor agent which is also present in normal kidneys. However, several other possibilities suggest themselves. The substance formed in the kidney with a defective blood supply might be somewhat different in chemical con-

stitution and therefore more active pharmacologically. It is also possible that the kidney with an impaired circulation is less capable of excreting the pressor substance than is the normal kidney, which forms it in equal amounts. Again, one can conceive of the pressor agent as a product of some intermediary metabolic process in the kidney, the reaction failing to go on to completion in the absence of an adequate blood supply. Furthermore, the possibility remains that the occurrence of an increased pressor activity in the ischemic kidney is purely incidental and bears no relation to the rise in blood pressure exhibited by the animal. Conclusions in regard to these questions as well as concerning the problem of the possible relation of the findings reported to renal hypertension in man cannot be drawn until further evidence is available.

SUMMARY

The administration of saline extracts of the kidneys of normal dogs to rats anesthetized with pentobarbital sodium usually causes a significant rise in blood pressure. Similar extracts of the kidneys of dogs rendered hypertensive by compression of the renal arteries cause a more marked increase in the blood pressure of the recipient animals. Comparisons of extracts prepared from the two kidneys of dogs rendered hypertensive by compression of one renal artery have shown a distinctly greater pressor effect from the abnormal than from the normal kidney. The possible relation of the findings to the mechanism of the hypertension produced by compression of the renal arteries has been discussed.

MULTIPLE MYELOMA

REPORT OF FOUR CASES, WITH HYPERPROTEINEMIA IN TWO

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AND
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Four patients with multiple myeloma of the plasma cell type were studied clinically and pathologically at the Montreal General Hospital during 1934 and 1935. The occurrence of unusual features, such as hyperproteinemia in two instances and absence of Bence-Jones protein in three instances, seemed to justify publication of a detailed report. The occurrence of these four cases within a period of eighteen months was of further interest, as no other established cases were recorded during the fifteen year period from 1921 to 1936.

REPORT OF CASES

CASE 1.—P. J., an Ethiopian aged 42, was admitted to the service of Dr. C. P. Howard on Aug. 6, 1935, complaining of weakness and pain in the lower portion of the back of three weeks' duration.

Family History.—His family history was not remarkable, in that his parents had died of unknown causes, and his brothers and sisters were alive and well.

Personal History.—The patient was born and bred in British Guiana. He worked as a police officer in Guiana, a miner in Nova Scotia and a laborer in Cuba and Montreal. He contracted pneumonia in 1913 and influenza in 1917 and was admitted to the Montreal General Hospital in 1927 with a diagnosis of duodenal ulcer and latent syphilis. After discharge he was treated for three years in the outpatient department of the hospital and was reported cured.

History of Present Illness.—The patient was in good health until three weeks before admission to the hospital, when he noticed slight stiffness and pain in the lower portion of the back on bending. The pain and weakness in the lumbar and sacro-iliac regions became more pronounced in spite of the application of a belladonna plaster. The day prior to his admission to the hospital he worked with pick and shovel until 2 p. m., when he had to be assisted home because of severe pain in his back.

Examination.—The temperature was 97 F., the pulse rate 72 and the weight 145 pounds (65.8 Kg.). The patient was a well developed and fairly well nourished Ethiopian. He appeared to have severe pain in the lumbar region on the slightest movement. The head, nose, throat and mouth were not remarkable. The lungs were clear. The heart was slightly enlarged, both to the right and to the left, and there was a localized apical systolic murmur. The blood pressure was 112

From the Department of Medicine and the Department of Pathology, the Montreal General Hospital.

systolic and 80 diastolic. The abdomen was normal. There was a purulent urethral discharge of gonorrheal etiology. Examination of the back revealed no tenderness over the spines of the vertebrae or the sacro-iliac joints. There was, however, pain in the lumbosacral region on the slightest movement.

Laboratory Data.—Urine: The urine was clear and had a specific gravity of 1.016. Neither albumin nor sugar was present. There were from 4 to 9 pus cells per high power field.

Blood: A blood count showed 3,320,000 red blood cells, 6,400 white blood cells and 70 per cent hemoglobin (Hellige). A differential count showed: polymorphonuclears, 67 per cent; lymphocytes, 27 per cent; eosinophils, 2 per cent and monocytes, 4 per cent. The van den Bergh test showed 0.2 units.

Chemical analysis of the blood showed: urea nitrogen, 11 mg.; creatinine, 1.96 mg.; uric acid, 5.71 mg., and sugar, 140 mg., per hundred cubic centimeters. The Wassermann reaction was negative. The complement fixation test for gonococci gave a positive reaction.

Spinal Fluid: The Wassermann reaction of the spinal fluid was negative, but the Pandy reaction was positive.

Diagnosis.—In view of the character of the pain and the chronic gleet, a diagnosis of gonorrheal arthritis was entertained. However, when roentgenograms of the area involved were taken, they showed multiple circumscribed rarefied areas suggestive of multiple myeloma. The subsequent investigation served to confirm this diagnosis.

Further Laboratory Data.—Roentgenograms: Further roentgenograms showed rarefied areas throughout the skull, vertebrae, pelvic bones, femurs and ribs. The pulmonary fields were clear. The tibias were not involved.

Metabolism: The basal metabolic rate was —11 per cent.

Blood: Further study of the blood was made:

	Nov. 12	Aug. 21	Aug. 26	Sept. 6
Total proteins, Gm. per 100 cc.	12.39	12.58	12.88	13.06
Albumin, Gm. per 100 cc.	2.45	2.96	2.87	
Globulin, Gm. per 100 cc.	9.59	9.96	9.77	
Fibrinogen, Gm. per 100 cc.	0.35	0.26	0.24	

The calcium content was 13 mg. and the phosphorus content 3.52 mg. per hundred cubic centimeters.

The Bence-Jones proteose was never demonstrated either in the urine or in the blood plasma, although an unidentified proteose was precipitated from both plasma and urine at 56 C.

A hemogram on August 28 showed: red blood cells, 2,720,000; white blood cells, 11,500; hemoglobin, 48 per cent; platelets, 126,000; reticulocytes, 0.5 per cent, and diameter of red cells, 8.4 microns.

A differential count showed: polymorphonuclears, 75 per cent; lymphocytes, 20 per cent; eosinophils, 2 per cent; monocytes, 1 per cent; myelocytes, 1 per cent, and metamyelocytes, 1 per cent.

The bleeding time was one and one-half minutes (Duke's method) and the coagulation time fifteen minutes (Lee and White). There was normal retraction of the clot. Study of the fragility of the erythrocytes showed that hemolysis began in 0.4 per cent solution of sodium chloride and was complete in 0.3 per cent solution. The plasma cell ratio was 77:23. The corrected sedimentation rate was 2.1 mm. per minute.

Course.—The disease continued to run an afebrile course. The patient's only complaint was of pain on movement. One rarefied area in the ninth rib on the right side became painful and tender on pressure. On September 3 a portion of this rib was removed for biopsy.

Biopsy.—Examination of the tissue removed from the ninth rib showed that the normal marrow was replaced by large and small cells, present in about equal numbers and having the same morphologic characteristics: (*a*) The large cells were round or oval, measuring from 10 to 18 microns in diameter, with an

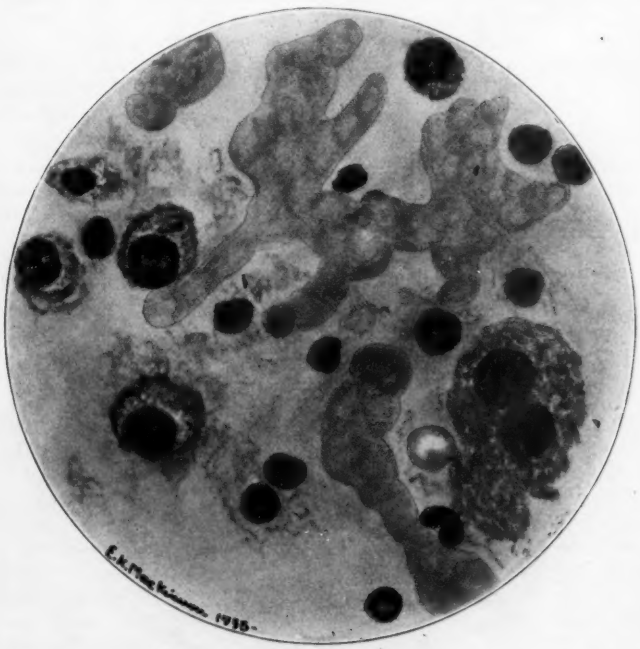

Fig. 1.—Camera lucida drawing of an actual field from a bone marrow smear, showing large and small plasma-like tumor cells. Their sizes may be compared with the size of the erythrocytes.

eccentrically placed hyperchromatic nucleus and nongranular, deep blue protoplasm. A number of these cells had two or three nuclei. Mitotic figures were present. (*b*) The smaller cells presented the same morphologic characteristics. Neither type of cell contained oxidase. Osteoclasts, many with inclusion bodies, were fairly numerous. No normal marrow tissue was present (figs. 1 and 2).

From October 11 to 25 the urine contained a large amount of coagulable protein, which partially disappeared at a temperature above 56 C. and reappeared on cooling below this temperature. However, during the last week of life the urine was entirely free from coagulable protein.

The patient rapidly became asthenic and died of bronchopneumonia on November 17.

Autopsy.—No lesions were noted except as hereafter outlined.

The lungs showed bilateral hypostatic bronchopneumonia.

The kidneys were of normal size, but the parenchyma was creamy pink, with a waxy appearance. Amyloid was not present. Microscopically, the femurs, the ribs, the vertebrae, the pelvic bones and, to a lesser extent, the skull showed extensive replacement of the medulla by islands of reddish gray tumor cells, similar to those described in the biopsy report. These islands averaged 1 cm. in diameter, although in places adjacent islands coalesced and formed larger tumor areas. The cortex of the long bones was not invaded.

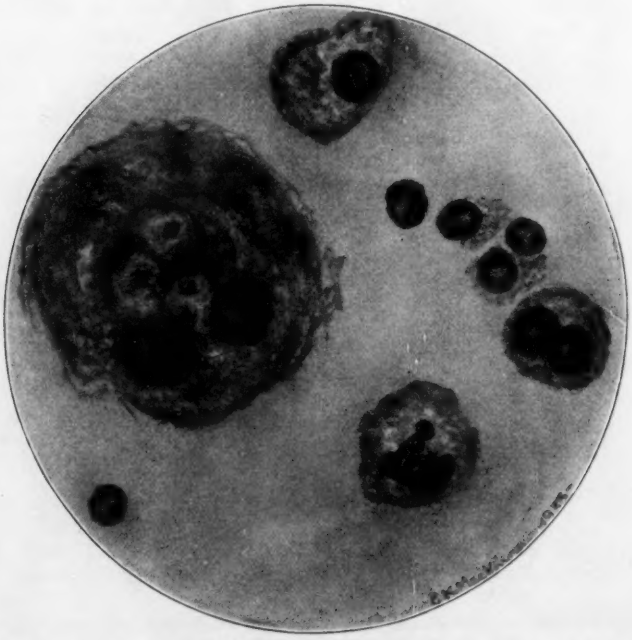

Fig. 2.—Another field from the smear shown in figure 1. The giant cell is believed to be an osteoclast.

CASE 2.—E. H., a man aged 37, was admitted to the Montreal General Hospital, in the service of Dr. L. C. Montgomery, on Sept. 9, 1934, complaining of pain in the right thigh of one year's duration and generalized weakness.

Personal History.—The patient was a Canadian physician, single, who enjoyed excellent health until 1933, when he contracted pneumonia. He had suffered since boyhood from periodic attacks of migraine, occurring about once a year.

History of Present Illness.—The patient enjoyed good health until December 1933, when atypical bilateral pneumonia (Streptococcus nonhaemolyticus) developed.

followed by phlebitis of the left saphenous vein He recovered slowly from this infection and remained in fairly good health until March 1934, when, after exposure, he had a second attack of pneumonia, localized in the base of the left lung and also followed by phlebitis of the right leg. The second attack of phlebitis persisted until July. Pain in the anterior aspect of the right thigh continued, however, and because of this he was admitted to the hospital.

Physical Examination.—The temperature was 98.2 F., the pulse rate 116 and the respiratory rate 20. The patient was well developed and well nourished, with a good color. The eyes, ears, throat and thyroid gland were all normal. There was no adenopathy. The lungs were clear, except for pleural thickening at the base of the right lung. The heart was not enlarged; no murmurs were noted. The blood pressure was 124 systolic and 88 diastolic. The abdomen and genito-urinary system presented no abnormality. Examination of the right leg and thigh revealed only atrophy of the quadriceps muscle, with some limitation in the right hip to flexion and abduction. No tenderness of the skull or ribs was noted.

Laboratory Data.—Urine: The urine showed good specific gravity. No sugar was present. There was 1+ albumin. Microscopically there was no blood or pus. Casts were found on one occasion (Sept. 15). Bence-Jones protein was never present (five tests).

Specimens of urine collected on September 20 and 21 showed a faint opalescence at 40 C., increasing at 60 C. No clearing occurred on further heating. The filtrate at 98 C. was clear and remained so when cooled to room temperature.

Blood: On September 11 examination showed: red blood cells, 3,600,000; white blood cells, 5,100; hemoglobin, 77 per cent (Hellige); diameter of red cells, 7.6 microns, and platelets, 274,000. The van den Bergh test showed 0.2 units.

A differential count showed: polymorphonuclears, 51 per cent; lymphocytes, 43 per cent; monocytes, 3 per cent, and eosinophils, 3 per cent.

The bleeding and coagulation times were normal. There was no tendency to excessive clotting or the formation of rouleaux.

Chemical study of the blood showed: urea nitrogen, 11 mg.; creatinine, 1.67 mg.; uric acid, 3.88 mg.; cholesterol, 211 mg., and sugar, 114 mg., per hundred cubic centimeters. No Bence-Jones protein was present. On September 17 there was 5.8 mg. of calcium and on September 20 11.9 mg. On September 17 there was 3.65 mg. of phosphorus and on September 20 3.09 mg. There were 8.9 units of plasma phosphatase (Kay's method). The plasma proteins (Kjehldahl method) showed: total protein, 12.39 Gm.; albumin, 3.22 Gm.; globulin, 6.58 Gm., and fibrinogen, 2.59 Gm., per hundred cubic centimeters.

Spinal Fluid: The spinal fluid showed a normal pressure. The total protein content was 0.04 Gm. per hundred cubic centimeters. The Wassermann reaction was negative. The colloidal gold curve was normal.

Metabolism: The basal metabolic rate was —7.

Roentgenograms: Roentgenograms were made of the skull, spine, ribs, pelvis and femurs. Through all the bones were innumerable irregular areas of osteoporosis, most extensive in the right pubic bone, the descending ramus of which was completely destroyed.

Diagnosis.—The diagnosis was multiple myeloma.

Clinical Course.—On October 1, a 5 inch (12.7 cm.) portion of the ninth right rib was removed with the patient under local anesthesia. The excised rib showed two localized tumor nodules, partially encapsulated and surrounded by areas of bone showing dissolution of trabeculae. The tumor nodules were composed of

fairly large round cells with pale-staining cytoplasm and a large vesicular eccentrically placed nucleus. Mitotic figures were fairly numerous. Although most of the cells were nongranular, a small proportion contained neutrophilic and eosinophilic granules.

During the succeeding month the patient complained of severe pain in the lower portion of the back. He became progressively weaker and died on November 3.

Autopsy.—Postmortem examination showed terminal bronchopneumonia, with old pleural adhesions at the base and infarction of the middle lobe of the right lung. There was also thrombosis involving the inferior vena cava and renal veins, with recent infarction of both kidneys. Microscopic examination of sections from all parenchymatous organs showed no evidence of tumor. Sections from the skull, vertebrae, pelvis, femur and ribs showed involvement of the bone by tumor, with destruction of osseous tissue about the tumor areas. The character of the tumor corresponded closely with that given in the biopsy report. Sections of the kidneys showed massive recent infarction with patchy tubular degeneration. A few tubules contained albuminous casts. The interstitial tissue was infiltrated by foci of lymphocytes.

CASE 3.—R. L., a soldier aged 26, single, was admitted to the Montreal General Hospital on Feb. 2, 1934, complaining of weakness, fever, loss of weight and pains in the back, neck, right leg and chest.

Family History.—The family history was irrelevant.

Personal History.—The patient was born in Montreal. He had never had any previous serious illness. He said he did not use alcohol but used tobacco moderately. He stated that he had not had a venereal disease.

History of Present Illness.—The patient was perfectly well until November 1933, when he awoke one morning with diarrhea and aching pains in the loins and lower lumbar region. After several days the symptoms disappeared, and he returned to work. At the end of December he suffered a recurrence of the pains in the lower part of the back and loins. After taking to bed on December 29 he experienced similar pain in the neck, in the right leg and behind the sternum. During the interval from December 29, until his admission to the hospital on Feb. 2, 1934, the course was rapidly down hill, the patient showing progressive weakness and loss of weight. His temperature varied from 99 to 102 F.

Examination.—The temperature was 101.2 F., the pulse rate 144 and the respiratory rate 20. The patient was a small, thin, pale man who looked ill. He held his head rigidly, owing to pain in the neck and back on movement. The eyes (including the fundi), ears, nose, throat and glandular system were not remarkable. The lungs were clear. The heart showed some enlargement to the right. There was a slight basal systolic murmur. The blood pressure was 124 systolic and 60 diastolic.

Examination of the abdomen, rectum, nervous system and genito-urinary tract revealed no abnormality. Tenderness was elicited over the chondrosternal junctions over the sternum and over the great trochanters but not elsewhere.

Laboratory Data.—Urine: Twenty-three specimens of urine were examined. The specific gravity was consistently low (1.002 to 1.012), sugar was never present and albumin was present in amounts varying from a trace to 1+. Microscopically a little pus was present in all specimens but no blood, and on five occasions there was a rare granular cast. Bence-Jones protein was never present.

Blood: The data on the blood were as follows:

	Feb. 2	Feb. 7	Feb. 22	March 3	March 31	April 25
Red blood cells, millions	2.2	1.86	1.27	1.94	1.81	1.67
Hemoglobin, %	36	30	25	38	..	30
White blood cells	17,600	7,450	11,050	6,800	7,800	19,850
Platelets, thousands	...	150	151	93	...	68
Reticulocytes, %	...	7.9	12.5	...	...	7.6
Polymorphonuclears, %	86	76	73	65	85	82
Lymphocytes, %	7	12	14	28	5	7
Eosinophils, %	0	5	..	1	..	1
Monocytes, %	4	..	3	2	1	0
Metamyelocytes, %	..	3	8	..	..	3
Myelocytes, %	2	..	2	2	2	3
Degenerates, %	..	4	..	..	..	4
Diameter of erythrocytes, microns	..	7.7	7.4	..	..	7.7

No Bence-Jones protein was present in the blood serum. Further chemical study showed: urea nitrogen, 17 mg.; calcium, 14.7 mg. on February 8 and 9.9 mg. on March 21; phosphorus, 2.43 mg.; cholesterol, 173 mg.; plasma protein, 6.23 Gm.; albumin, 3.99 Gm.; globulin, 1.61 Gm., and fibrinogen, 0.63 Gm., per hundred cubic centimeters.

Electrocardiogram: Abnormal ST waves indicated myocardial changes.

Wassermann Tests: The Wassermann reaction of the blood and of the spinal fluid was negative.

Roentgenograms: Roentgenograms were made of the pelvis, femurs, ribs and cervical, dorsal and lumbar regions of the spine. These showed destructive lesions involving the vertebral bodies, the ribs, the pelvic bones and the femurs suggestive of metastatic carcinoma.

Diagnosis.—The first diagnosis considered was streptococcic septicemia. After the roentgenographic report had been given a complete clinical and laboratory investigation was undertaken to determine a possible primary malignant process, but none was found. The diagnosis of multiple myeloma was arrived at by a process of exclusion.

Clinical Course.—The patient continued to fail progressively from the time of his admission to the hospital on February 2 until his death on April 27. His temperature showed a daily elevation as high as 103 F. occasionally. Morphine was required daily for the pain in the neck and the lower part of the back. Toward the end of March pressure paraplegia developed at the level of the fifth thoracic segment. General anasarca appeared. Shortly before death occurred large bluish elevated swellings appeared in many of the costal cartilages and at the costochondral junction of the twelfth rib.

Autopsy.—Postmortem examination revealed generalized anemia. No notable abnormalities were seen in the parenchymatous organs, except the slight cloudy swelling and mild inflammatory reaction of polymorphonuclear cells about the basophilic cellular débris in the tubules. The kidneys weighed 130 and 135 Gm., respectively. The lesions in the bones were extensive, the sternum and bodies of the four lumbar vertebrae being almost entirely destroyed. In general, the histologic appearance resembled that in the crest of the left ilium, which was as follows: Only small patches of bony tissue remained. Surrounding and replacing these were solid masses of cells of two chief varieties: (1) large oval cells, having a pale basochromic vesicular nongranular cytoplasm and an eccentrically placed large nucleus containing a central nucleolus, and (2) small cells differing from the larger cells chiefly in magnitude. Many large syncytial cells were also present. These were multinucleate and were considered to be osteoclasts. The only site of tumor, other than that in the long bones, was in the retroperitoneal glands near the pancreas and in the bifurcation of the aorta, which showed replacement by

tumor tissue of a type similar to that in the bones. In the midthoracic region was an area of complete absorption of the vertebral body, with involvement of cartilage, fibrous tissue proliferation and pressure involvement of the spinal cord.

CASE 4.—R. M., a Canadian man of 69 years, was admitted to the service of Dr. C. P. Howard on October 9, 1935, complaining of renal and thoracic difficulties.

Family History.—The family history was irrelevant.

Personal History.—The patient was born in Quebec and worked as a farmer and sawmill operator. He was single, had never had venereal disease and had not used alcohol or tobacco to excess. He had never been ill until the onset of the present illness, except for typhoid when he was a young man.

Present Illness.—The patient had enjoyed good health until two years before admission to the hospital, when he first began to complain of pain in the lower part of the back after any heavy lifting. For a month he had vomited frequently after meals. He had also had a great deal of pain in the right side of his back. He had had nocturia (urinating three or four times per night) for many years. During the past month he has been confined to bed because he was too weak to walk.

Examination.—The temperature was 102 F., the pulse rate 108 and the respiratory rate 24. The patient appeared thin and sallow. The breathing was irregular and grunting, owing to substernal pain. The mental state seemed somewhat clouded. The left pupil was larger than the right and reacted sluggishly to light and in accommodation. Coarse moist râles were present throughout the lungs, and there was dulness in both axillae. The heart was slightly enlarged to the left. The blood pressure was 144 systolic and 60 diastolic. Many of the ribs were tender posteriorly, particularly on the left side. The abdomen was normal. The tendon reflexes were all present and normal.

Laboratory Data.—Urine: The urine showed a heavy precipitate of coagulable protein on heating. This protein disappeared on further heating and reappeared on cooling to 56 C. This reaction was entirely reversible. The urinary sediment showed a few cellular and granular casts.

Blood: Examination of the blood showed: red cells, 3,500,000; leukocytes, 2,300; hemoglobin, 67 per cent (Hellige); platelets, 208,000; erythrocytic diameter, 7.9 microns; reticulocytes, 0.5 per cent; polymorphonuclears, 83 per cent; lymphocytes, 16 per cent, and monocytes, 1 per cent. The myeloid cells were nearly all immature polymorphonuclear cells. They showed basophilic degeneration of the granules but were not basophils. The Wassermann reaction was negative.

Chemical study of the blood showed: urea nitrogen, 31 mg.; creatinine, 3.26 mg.; sugar, 164 mg.; cholesterol, 129 mg.; uric acid, 3.1 mg.; phosphorus, 5.26 mg.; calcium, 14.8 mg.; total protein, 7.7 Gm.; albumin, 5.04 Gm.; globulin, 1.06 Gm., and fibrinogen, 1.6 Gm. The van den Bergh test showed 1 unit.

Electrocardiograms.—Electrocardiograms showed a prolonged conduction time.

Roentgenograms: Roentgenographic study of the ribs, the vertebrae, the bones of the shoulder girdle, the pelvis and the femurs revealed discrete and confluent circular areas of destruction, most numerous in the ribs, many of which showed pathologic fractures.

Diagnosis.—The diagnosis was multiple myeloma.

Clinical Course.—The patient died of acute bronchopneumonia on October 12, three days after admission to the hospital.

Autopsy.—Postmortem examination revealed generalized advanced arteriosclerosis, pneumonia of the lower lobe of the left lung, passive congestion of the lungs and liver and multiple osseous tumors. The kidneys weighed 150 and 200 Gm.,

respectively. Microscopically the parenchymatous tissue showed marked degenerative changes. Many of the glomeruli were hyalinized. The tubular epithelia showed degeneration, with granular and hyaline casts filling the lumens of the tubules. No productive changes were present in the stroma.

TABLE 1.—*Data for Four Patients with Multiple Myeloma*

	Case 1	Case 2	Case 3	Case 4
Age at onset	42 years	37 years	26 years	69 years
Sex	Male	Male	Male	Male
Duration of illness	4 months	11 months	5 months	24 months
Presenting symptoms				
Pains in lower part of back	Present, 3 wk.	Not present	Present, 3 mo.	Present, 2 yr.
Pains in legs	Absent	Present	Absent	Absent
Weakness	Present, 4 mo.	Present, 11 mo.	Present, 5 mo.	Present, 2 yr.
General osseous pain	Absent	Absent	Present	Absent
Condition on admission				
Emaciation	None	None	Present	Present
Cachexia	None	None	Present	Present
Pallor	None	None	Present	Present
Pain on movement	Lumbosacral	Right hip	Head and extremities	Ribs
Urine				
Albumin	Trace, 7 or 15 tests	1+ at times	Trace to 1+	1+
Casts	Once	Once	Rare, 5 times	Many
Sugar	Never	Never	Never	Never
Bence-Jones protein	Never	Never	Never	Present
Proteose unidentified	Present	Never	Never	None
Blood				
Anemia	Hyperchromic, moderate	Hypochromic, moderate	Hypochromic, moderate	Hypochromic, moderate
Leukocytes	Normal at first; later increased	Normal	Normal at first; later increased	Leukopenia
Platelet count	Low	Normal	Low	Normal
Differential count	Normal	Normal	Myelocytes, 2-3%	Normal
Van den Bergh test	Normal	Normal	Normal	Normal
Sedimentation rate	Very rapid	Rapid	Not tested	Not tested
Chemical study of blood				
Uric acid	High	Normal	Normal	Normal
Total protein	High	High	Normal	Normal
Albumin-globulin ratio	Complete reversal	Complete reversal	Normal	Globulin low
Bence-Jones protein	Absent	Absent	Absent	Not tested
Calcium	High	Low; then high	High; then low	High
Phosphorus	Normal	Normal	Normal	High
Involvement of bone (roentgen evidence)				
Spine	Present	Present	Present	Present
Pelvis	Present	Present	Present	Present
Ribs	Present	Present	Present	Present
Skull	Present	Present	Not studied	Not studied
Femurs	Present	Present	Present	Present
Tibias	None	None	Not studied	None
Humerus	None	None	Not studied	Present
Lung	None	None	None	None
Postmortem data				
Lungs	Terminal pneumonia	Terminal pneumonia; infarction of lung	Congested	Pneumonia
Liver	Normal	Normal	Normal	Congested
Spleen	Normal	Normal	Normal	Congested
Kidneys	Normal	Infarction	Swelling; degeneration	Hyaline degeneration
Type of lesion in bones	Typical	Typical	Typical	Typical
Retroperitoneal glands	No tumor	No tumor	Tumor present	No tumor

Sections of the sternum, pelvis, spine, skull, ribs and sphenoid bone were examined. All except the skull showed replacement of the marrow by islands of tumor tissue. The marrow of the sternum, ribs, vertebrae and pelvic bones was largely replaced by tumor tissue. Microscopically this tumor tissue consisted of large and

small plasma-like cells with large eccentric nuclei and nongranular basochromic protoplasm. Many of the cells contained nucleoli, and some were multinucleate. Osteoclasts were not numerous. The tumor cells all showed a negative reaction for oxidase.

COMMENT

The following summary of the data for our four patients shows certain interesting and unusual features, although none of these is foreign to the literature of the disease.

Age and Sex.—Multiple myeloma is a disease of later life. Only five instances have been reported in which the patient was less than 35 years old, and for two of the patients there was no microscopic proof of myeloma, as noted by Geschickter and Copeland [1] in their comprehensive monograph. The ages of the patients who were shown to have myeloma were 30, 27 and 22 years, respectively. One of our four patients was 26 years of age, and the second was only 37. All four were men.

Etiology.—Careful scrutiny of the clinical histories of our patients failed to reveal pertinent information relative to the etiology of the disease. The first patient was a Negro laborer born in British Guiana. The other three were native-born Canadians; one was a professional soldier, one a physician and one a farmer and sawmill operator. The Negro laborer had latent syphilis; but this disease had been successfully treated and at the time of his admission to the hospital the Wassermann reaction of the blood was negative. The family history did not record relevant facts. A history of trauma was not elicited in any of the cases.

Clinical Features.—The duration of the illness from the onset of symptoms until death was four, five and eleven months, respectively, for the younger patients but somewhat longer for the 69 year old patient. The outstanding clinical symptoms on entry, in common with those of the vast majority of patients with the disease, were pain and weakness. The pain occurred in the lower lumbar or sacral region of the back in three of the four patients and in the lower extremities in two, but generalized osseous pain was noted in only one. Weakness was an outstanding symptom, having been present in these patients even before the onset of the pain. Sharp accentuations of pain and periods of remission were noted by three of the four patients. Severe pain on movement was noted by all four. In one instance its site was the lumbosacral region; in a second, the right hip; in a third, the head and extremities, and in the fourth, the ribs.

Physical examination of the patients in all instances revealed surprisingly little information so far as diagnostic features were concerned. Perhaps the pain in the back and weakness should have suggested the

1. Geschickter, C. F., and Copeland, M. M.: Multiple Myeloma, Arch. Surg. **16**:807 (April) 1928.

possibility of this disease to the clinician, but invariably it was the roentgenogram which pointed to the correct diagnosis. None of the patients when first observed had sufficient osseous destruction to produce deformity, pathologic fracture or even egg-shell crackling, although two patients eventually showed tumors of the ribs and sustained pathologic fractures. Pressure paraplegia was a terminal complication in one patient. The blood pressure was always within normal limits.

Laboratory Data.—The urine of only one of the four patients showed Bence-Jones protein, although the other three patients were under observation for long periods and many urinalyses were made. In the urine of one patient (case 1) an unidentified proteose was observed on several occasions. Albumin, casts and blood cells were not more frequently found than would be expected in any progressive malignant process. At no time were there sufficient urinary findings to suggest the presence of nephritis.

The examination of the blood showed moderate anemia in all cases. In the first patient it was of the hyperchromic type, with definite macrocytosis, the modal erythrocyte having a diameter of 8.4 microns. In the other three patients the anemia was of the hypochromic type. In two patients the leukocytes were normal at first, but moderate leukocytosis developed later. The fourth patient had terminal leukopenia. The differential count was within normal limits for three patients. The third patient occasionally showed 2 or 3 per cent myelocytes. The platelet counts were normal for two patients and low for the other two. The sedimentation rate was rapid in one.

In summary it may be stated that the hemogram failed to show any characteristic feature. Emphasis is placed on the absence of immature myeloid cells in all but one patient, although many studies were made. This finding is counter to the prevalent opinion, although actual statistics show that only one patient in four shows myelocytes in the peripheral blood.

Chemical study of the blood revealed that one of the unusual, though not unique, features in two of the patients was hyperproteinemia. This increase in the plasma protein content was due, in both instances, to an increase in the globulin content. In the second patient an increase in the fibrinogen content also occurred. In contrast to the increased globulin content, the albumin content was reduced to approximately half the usual value. No determination of the osmotic pressure of the plasma was made, but tissue edema did not occur. Consequently it may be assumed that the osmotic pressure of the plasma was not greatly reduced. The hyperglobulinemia probably compensated in part for the lack of serum albumin. It was of further interest that the only patient who showed Bence-Jones protein had neither hyperproteinemia nor hyperglobulinemia. None of the patients showed abnormally rapid coagulation or a

tendency to rouleaux formation, although the thrombophlebitis in the third patient was suggestive. In fact, the first patient showed a slight prolongation of the coagulation time (Lee and White method). However, the corrected sedimentation rate (Ernstene and Rourke method) was 2.1 mm. per minute, an unusually high figure. The occurrence of hyperproteinemia in multiple myeloma is infrequent, as determined from a study of the literature up to 1935. Sweigert [2] was able to collect reports of only sixteen instances of hyperproteinemia prior to his own, in approximately five hundred reports of cases of the disease, although he was able to find reports of only thirty-five cases of multiple myeloma in which a satisfactory quantitative investigation of the plasma proteins had been made. The presence of an unidentified proteose in the urine and blood plasma, as in our first patient, has been considered by some authors [3] to possess the same diagnostic significance as Bence-Jones protein. In the reports of cases of hyperproteinemia in multiple myeloma the excessive quantities of protein have been said to be either some form

TABLE 2.—*Data on Plasma Proteins*

	Case 1	Case 2	Case 3	Case 4
Total proteins, Gm. per 100 cc.....	12.58	12.39	6.23	7.70
Serum albumin, Gm. per 100 cc.....	2.36	3.22	3.99	5.04
Serum globulin, Gm. per 100 cc.....	9.96	6.58	1.61	1.06
Fibrinogen, Gm. per 100 cc.....	0.26	2.59	0.63	1.60
Bence-Jones protein	Absent	Absent	Absent	Present
Unidentified proteose	Present	Absent	Absent	Absent

of globulin or actual Bence-Jones protein. In only one instance (the patient reported on by Reimann [4]) was an excess of fibrinogen found. Our second patient was therefore almost unique in this respect, showing an excessive amount both of globulin and of fibrinogen. Table 2 is a summary of the plasma protein values for our four patients.

Course of the Disease.—All four patients eventually revealed the progressive changes common to all forms of malignant disease. The third patient had a high fever for many weeks. The spine, bones of the pelvis, femurs and ribs of all the patients were extensively involved. Roentgenograms of the skull were not made in two cases, but those for the first and second patients showed typical lesions. The immediate cause

2. Sweigert, C. F.: Multiple Myeloma with Hyperproteinemia, Am. J. M. Sc. **190**:245, 1935.

3. Rosenblum, A. H., and Kirshbaum, J. D.: Multiple Myelomas with Tumor-Like Amyloidosis: A Clinical and Pathologic Study, J. A. M. A. **106**:988 (March 21) 1936.

4. Reimann, H. A.: Hyperproteinemia as a Cause of Autohemagglutination: Observations in a Case of Myeloma, J. A. M. A. **99**:1411 (Oct. 22) 1932.

of death in three of the four patients was pneumonia. Infarction of the lung and the kidneys of the second patient was also noted post mortem.

Autopsy.—The postmortem data may be separated into two groups: those regarding the lesions in the bones and those regarding the parenchymatous organs, in a measure secondary to the tumor itself.

(*a*) Pathologic changes not directly due to the tumor were present in the lungs and in the kidneys. Three of the four patients showed a terminal bronchopneumonic process. The second patient had saphenous and femoral thrombophlebitis which extended into the inferior vena cava and involved both renal veins. There was also infarction of the middle lobe of the right lung, probably secondary to the thrombotic process in the inferior vena cava. The renal lesions were of interest because nephritis has been frequently reported in this disease. Geschickter and Copeland [1] observed nephritis of the nephrosis type in about 60 per cent of one hundred and fifty patients. Ninety-two patients had nephritis and Bence-Jones protein, thirty-seven had nephritis alone and in only five were both nephritis and Bence-Jones protein absent. These data suggest some connection between the proteinuria and the lesions in the kidney. Bell,[5] on the other hand, concluded from a study of eleven patients that renal insufficiency in multiple myeloma is due in a majority of instances to vascular degeneration, pyelonephritis incident to "cord bladder" or prostatic hypertrophy.

Renal insufficiency was not a feature in any of our four patients, although our second patient had terminal infarction of both kidneys. The kidneys of the first patient were normal. Mild degenerative changes were present in the kidneys of the third and fourth patients, although only one patient had Bence-Jones proteinuria. These data support the contention that proteinuria is not an important cause of the tubular degeneration.

(*b*) The tumor as observed in biopsy sections and post mortem presented all the gross and microscopic features characteristic of multiple myeloma of the plasma cell type. The tumor cells of all four patients presented a similar histologic appearance. They resembled plasma cells only in shape and in the eccentric position of the nucleus. Otherwise they presented the characteristics of a rapidly proliferating neoplasm. Mitotic figures and large multinucleated cells were numerous. The accompanying camera lucida drawings of actual fields in the biopsy specimens from the first patient illustrate the histologic features of the tumor cells. The large cell with inclusion bodies is an osteoclast, not a tumor cell. Metastases to parenchymatous organs or lymphatic vessels were searched for but observed only in the third patient, who showed

5. Bell, E. T.: Renal Lesions Associated with Multiple Myeloma, Am. J. Path. **9**:393, 1933.

involvement of the retroperitoneal glands. Direct extension of the tumor from the vertebrae seemed unlikely, as the involved glands were not contiguous to the invaded bone.

SUMMARY

Four patients with multiple myeloma of the plasma-like cell type were studied by clinical and laboratory methods and eventually subjected to complete postmortem examination. The first patient was admitted because of pain in the lower part of the back of three weeks' duration, but he had worked with pick and shovel the day prior to admission to the hospital. The disease was considered to be arthritis associated with chronic gleet until a roentgenogram showed lesions suggestive of multiple myeloma. Moderate hyperchromic anemia, hyperglobulinemia and an unidentified proteose in the blood and urine were noted. The patient died of bronchopneumonia one month after admission to the hospital.

The second patient was hospitalized because of pain in the thigh following two attacks of pneumonia complicated by phlebitis. The diagnosis was again suggested by the appearance of the roentgenograms. There were moderate hypochromic anemia and hyperfibrinogenemia as well as hyperglobulinemia. Death followed thrombosis of the inferior vena cava, with infarction of both kidneys and a portion of the right lung. The tendency to venous thrombosis in the presence of hyperproteinemia is recognized and may have been an important factor, although no change in the coagulability of the blood was noted.

The third patient was admitted because of generalized osseous pain, high fever, severe anemia and leukocytosis. A tentative diagnosis of atypical subleukemic myelosis or streptococcic septicemia was made. The diagnosis ultimately rested between carcinomatosis and multiple myeloma. The problem was finally settled by biopsy of a tumor in one rib. No changes in the blood proteins were found. The disease eventually caused pressure paraplegia, and there was metastasis to the retroperitoneal lymph nodes.

The fourth patient, the only one to show the Bence-Jones protein, was an old man who was admitted because of bronchopneumonia. He had been in failing health for a month, although he had had pain in the back for two years. The diagnosis of multiple myeloma was suggested when the urine was examined and later was confirmed by roentgenograms of the spine and pelvis. The blood showed moderate anemia but no hyperproteinemia.

It is evident from a study of these four patients that multiple myeloma of the plasma cell type may or may not be accompanied with changes in the plasma proteins or with the appearance of proteose or Bence-Jones proteinuria and further that these changes, when present, bear no definite relation to degenerative changes in the kidney.

CONCLUSIONS

Weakness and pains in the lower portion of the back are the most constant symptoms of multiple myeloma.

Frequently no characteristic clinical signs and symptoms are noted until the disease is far advanced, although the combination of weakness, persistent pain in the back and anemia is suggestive of the disease.

The diagnosis can usually be made roentgenographically on the basis of the punched-out areas of rarefaction in the pelvic bones, vertebrae or skull.

The presence of Bence-Jones protein or some type of proteose in the blood and urine is of diagnostic value, but many patients with the disease show neither.

Hyperglobulinemia with or without an increase in the fibrinogen content is probably more common than a survey of the literature indicates and may predispose to venous thrombosis.

Anemia is almost always present; it may be severe and either hyperchromic or hypochromic.

Metastases are unusual but may occur to the retroperitoneal glands.

Clinically, evidence of degenerative changes in the kidneys is often lacking or insignificant.

SIGNIFICANCE OF HEMOLYTIC STREPTOCOCCIC BACTEREMIA

A STUDY OF TWO HUNDRED AND FORTY-SIX PATIENTS

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The prognosis in infection due to hemolytic streptococci depends on the summation of such factors as the age of the patient, the location and type of the infection, the presence or absence of debilitating disease and bacteremia. For several years we have been interested in assessing the relative importance of these various factors in hemolytic streptococcic infection. At present we are reporting the results of a study of 246 patients with hemolytic streptococcic bacteremia, together with some of our observations concerning the variation in the organisms producing these infections and the defense mechanism of the host.

In general, bacteremia may be interpreted as due to a loss of equilibrium between the normal clearing mechanism of the body and the local defense mechanism. In the case of hemolytic streptococcic bacteremia there are reasons for believing that bacteremia results from the invasive properties of this particular species of organism and differences in the defense mechanism of the host.

ANALYSIS OF CASES

Seasonal Incidence.—As might be anticipated, the highest incidence of bacteremia was observed during the months when hemolytic streptococcic infections are most prevalent, that is, from January to May.

Age of the Patients.—The age distribution for patients with bacteremia fell into three distinct groups: The first, representing the patients in the first two decades of life, included most of the patients with bacteremia arising from infections of the throat and middle ear, including lateral sinus thrombosis, cavernous sinus thrombosis and thrombophlebitis of the deep tonsillar veins. The second group included

Read before the Association of American Physicians, May 5, 1937.

From the Thorndike Memorial Laboratory, the Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

the patients with puerperal infections, most of whom were observed between the ages of 20 and 40 years. Finally, the third group was made up of patients with cellulitis, most of whom were over 40 years of age. This distribution is shown in chart 1.

Mortality According to Age Distribution and Portal of Entry.—The relation of the incidence and fatality rate to these two factors is shown in charts 2 and 3. From chart 2 it may be seen that the fatality rate definitely increases with age and, while it is high in all decades, it is particularly noticeable that for patients over the age of 20 the number of deaths increases. When the three major groups are studied separately, as shown in chart 3, it is seen that the increasing fatality not only varies with the age of the patient but with the localization of the primary infection. It was lowest for the patients with

TABLE 1.—*Type of Infections*

	Total Number of Cases	Total Number of Fatal Cases	Fatality, Percentage
Primary infections			
Infections of throat, middle ear and mastoid, including thrombosis of lateral sinus, cavernous sinus and tonsillar vein	60	33	55
Pelvic infections	41	23	56
Cellulitis and erysipelas	61	49	80
Streptococcic infections secondary to			
Pneumonia	18	15	83
Diabetes	10	9	90
Tuberculosis	6	5	83
Operative treatment	22	20	90
Arteriosclerosis	19	18	95
Total	246	177	72

infections of the throat, middle ear and mastoid during the first two decades of life, while it was highest in all age periods for patients with cellulitis and erysipelas. The total fatality rate is given in table 1; this has been presented regardless of the ages of the patients. Here again, it is plain that the highest mortality occurred among patients with cellulitis and erysipelas and those with debilitating diseases, whereas for the other infections the percentage of fatality was lower.

Focal Lesions.—One of the characteristic features of hemolytic streptococcic infection with bacteremia is the relative infrequency of metastatic lesions in the form of abscesses. This series of patients was no exception to that well recognized fact. The various metastatic lesions which were observed are listed in table 2. The commonest suppurative lesions were in the joints, the subcutaneous tissues and the endocardium. Miscellaneous features are also listed in table 2. They comprise a large group but, on the whole, were infrequent. Sixty-two per cent of all the patients showed no metastatic lesions. The comparatively small number of patients with focal lesions is probably due, in part at least,

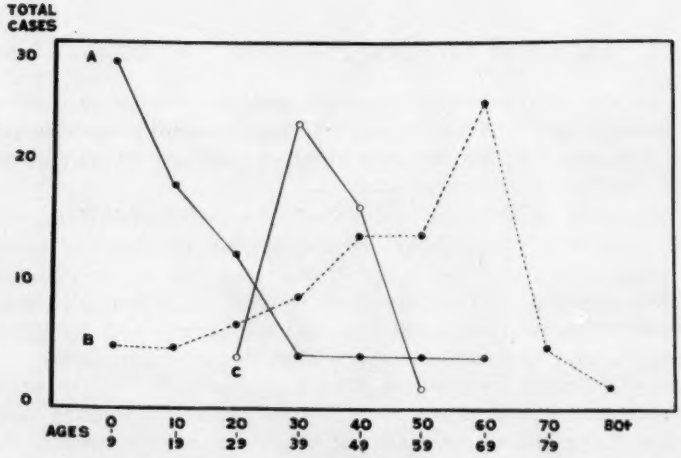

Chart 1.—Age distribution for patients with bacteremia according to the portal of entry. *A* indicates infections of the throat, middle ear and mastoid; *B*, erysipelas and cellulitis; *C*, puerperal sepsis.

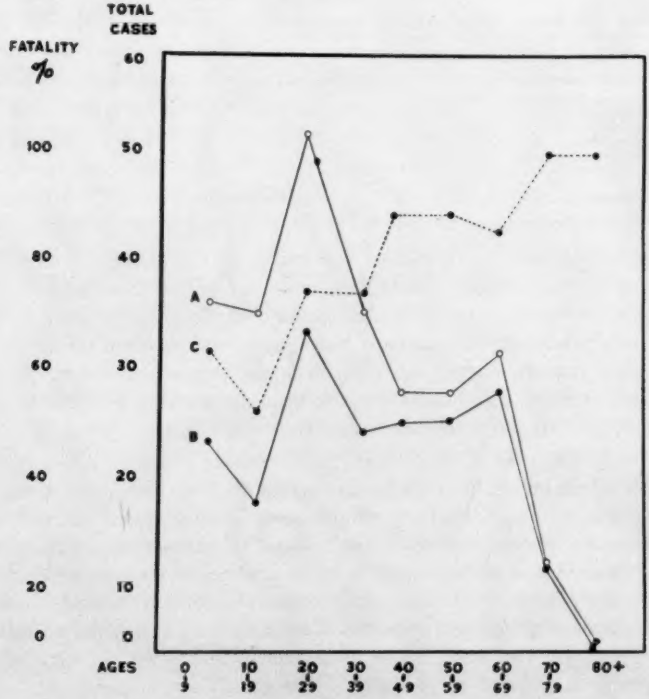

Chart 2.—Age distribution of patients with bacteremia, the total number of patients of each decade who died and the percentage of deaths for each decade. *A* indicates the total number of patients in each decade; *B*, the number of patients who died, and *C*, the percentage of deaths in each decade.

to the rapid course of the infection, together with the character of the infecting organism, as it produces substances which dissolve fibrin, kills leukocytes and in this way prevents the local defense mechanism

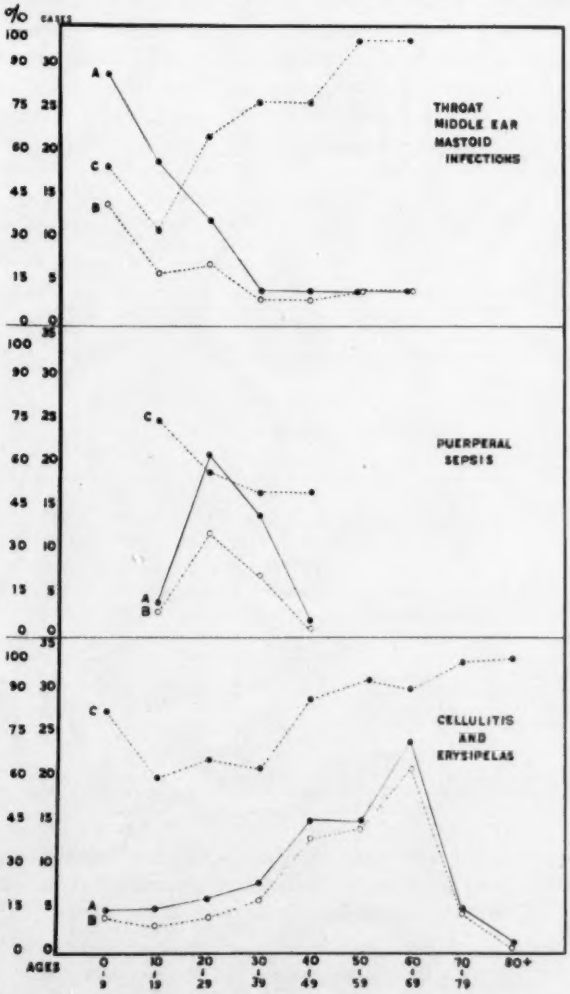

Chart 3.—The total number of patients with bacteremia arising from various foci of infection in different decades of life, together with the total number and the percentage of deaths in each decade. *A* indicates the total number of patients; *B*, the total number who died, and *C*, the percentage of deaths.

from becoming effective and fully operative. In table 3 the duration of the illness in patients with bacteremia is summarized. In the majority of patients the illness was of relatively short duration. Those surviving longer than from twenty to thirty days usually have focal lesions which gradually subside spontaneously or after the surgical drainage of an abscess. In chart 4 the data for a group of patients has been charted, showing the rapidly progressing type of sepsis, with fatal outcome within a few days. In chart 5 it may be seen that for other patients who show bacteremia at the beginning of the illness, if the blood stream

TABLE 2.—*Mortality Statistics*

	Total Number of Cases	Number of Recoveries	Number of Deaths
Metastatic lesions			
Arthritis	49	20	29
Subcutaneous abscesses	17	7	10
Endocarditis	11	0	11
Osteomyelitis	4	2	2
Abscess of lung	3	0	3
Empyema	5	2	3
Miscellaneous lesions			
Nephritis	4	0	4
Jaundice	7	0	7
Peritonitis	7	0	7
Abscess of spleen	1	0	1
Agranulocytosis	3	0	3
Mediastinitis	2	0	2
Meningitis	3	0	3
None	183	39	114

TABLE 3.—*Duration of Illness*

Duration of Illness, Days	Number of Fatalities	Number of Recoveries
Less than 10	85	19
11-20	49	11
21-30	23	9
31-40	4	3
41-50	9	8
51 +	7	19
Total	177	69

is cleared of organisms and if focal abscesses develop and can be treated surgically, recovery takes place. In chart 6 data for a group of patients are recorded showing temporary bacteremia, clearing of the blood stream without focal infection in all but 2 patients and recovery.

The charts show that the following sequence of events may occur: First, there may be a temporary invasion of the blood, with rapid clearing, no metastases and recovery. Second, after the bacteremia the blood may be cleared of organisms, and focal metastases may be set up in various areas, usually the joints, subcutaneous tissues or other organs. The outcome may be favorable if the abscesses can be drained adequately by surgical procedures, or a fatal outcome may result if the

abscesses are widespread and cannot be effectively treated. Finally, there may be rapidly progressive bacteremia without focal lesions, death resulting within a relatively short time.

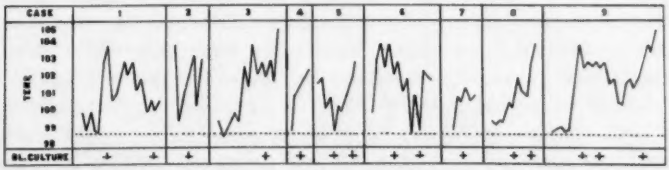

Chart 4.—Temperatures (F.) of patients with rapidly progressing bacteremia without localization. The arrow indicates the time of parturition in a patient in whom peritonitis developed.

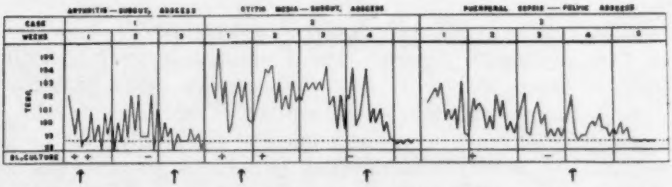

Chart 5.—The course of hemolytic streptococcic infection with bacteremia in 3 patients. The bacteremia was followed by clearing of the blood stream and abscess formation. Recovery followed drainage of abscesses. The arrows indicate the drainage of the abscesses.

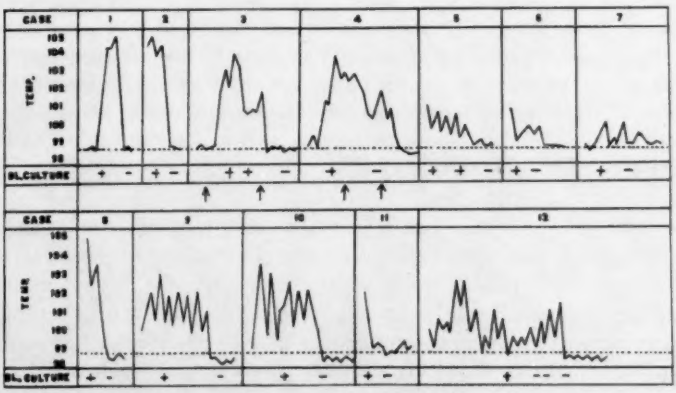

Chart 6.—Temperatures of patients with hemolytic streptococcic bacteremia for whom culture of the blood was made. Death occurred in 9. The blood was cleared promptly in all but 2 patients without abscess formation. The arrows indicate the time of incision of an abscess.

CHARACTERISTICS OF THE ORGANISMS CAUSING BACTEREMIA

To supplement the clinical observations and to obtain more information concerning the mechanism of bacteremia, we studied a small group of patients with hemolytic streptococcic bacteremia and compared the findings with those for a group of patients with hemolytic streptococcic infections without bacteremia. This study was concerned with the characteristics of the organisms and the immune response of patients with local and general infections.

In 8 patients with bacteremia it was found that the organisms all belonged to group A of Lancefield, and they were all beta hemolytic streptococci. Fibrinolysin and erythrogenic toxin were produced by all the strains, and they were all M strains, according to the classification of Ward and Lyons.[1] These organisms were not typed, because typing serum was not available.

To determine the capacity of these organisms to resist phagocytosis in normal blood, bactericidal tests with whole blood were made. It was ascertained that only one of the eight strains was phagocytosed and killed in moderate degree by normal blood. While this is not a particularly good method of testing the relative virulence of the various strains of hemolytic streptococci, it serves as a test that can be used for normal persons and for patients with infections in order to determine the bactericidal power of the whole blood against homologous as well as heterologous strains of hemolytic streptococci.

When these results were compared with those obtained from a study of the bactericidal power of the same controls with the organisms isolated from patients with local lesions without bacteremia, it was found that the blood of control subjects was capable of killing a number of the strains which were isolated from local lesions. These observations can be taken as an indication of the variation in the bactericidal power of the blood of normal persons for various strains of hemolytic streptococci; the blood of some healthy persons is capable of killing varying numbers of virulent hemolytic streptococci in vitro.

BACTERICIDAL POWER OF BLOOD OF PATIENTS WITH BACTEREMIA

When micro-organisms are growing rapidly in one or more foci of infection and overflowing into the blood faster than the clearing mechanism can eliminate them, bacteremia follows. At present it is generally believed that the most important groups of cells in removing organisms from the circulating blood are the cells of the reticulo-endothelial system. Moreover, it is well known that the efficiency of these cells in

1. Ward, H., and Lyons, C.: Studies on the Hemolytic Streptococcus of Human Origin: I. Observations on the Virulent, Attenuated, and Avirulent Variants, J. Exper. Med. **61**:515, 1935.

removing bacteria from the circulating blood and preventing secondary waves of bacteremia can be enhanced by introducing specific antibodies into the circulating blood or by a process of conditioning these cells through the previous immunization of the animal. That these cells can remove bacteria from the circulating blood while it is not possible to demonstrate the presence of antibodies has been amply demonstrated by Teale.[2] It also has been clearly shown by McMaster and Hudack [3] that antibodies develop locally in some tissues and in a higher concentration than exists in the circulating blood. It follows then that it is possible for the blood to be cleared of bacteria so that even specific antibodies cannot be demonstrated therein. However, it was of some interest to us to test the blood of patients with bacteremia for antibodies and compare the results with those for patients with local lesions without bacteremia.

TABLE 4.—*Bactericidal Power of the Blood of Eight Patients with Hemolytic Streptococcic Bacteremia* *

Case	Maximum Number of Organisms Killed by 0.5 Cc. of Blood		Outcome	Disease
	Cases	Controls		
1	10^{-4}	10^{-7}	L	Erysipelas
2	10^{-4}	10^{-7}	L	Pneumonia and empyema
3	10^{-4}	10^{-7}	L	Puerperal sepsis
4	10^{-7}	10^{-7}	D	Puerperal sepsis
5	10^{-4}	10^{-7}	D	Thrombophlebitis of jugular vein
6	10^{-2}	10^{-4}	D	Postoperative sepsis with multiple abscesses
7	10^{-2}	10^{-7}	L	Recurrent erysipelas
8	10^{-1}	10^{-7}	D	Puerperal sepsis with multiple abscesses

* 10^{-7} indicates from 2 to 10 organisms per 0.1 cc.; L, living, and D, died.

The methods for studying the bactericidal power were the same as previously reported.[4] The results of the study are recorded in table 4. Seven of the 8 patients with streptococcic bacteremia had antibodies,

2. Teale, F. H.: Some Observations on the Relative Importance of the Reticulo-Endothelial Tissues and the Circulating Antibody in Immunity: I. Bacterial Immunity in Relation to the Rôle Played by the Circulating Antibody and the Tissues Following Intravenous Introduction of the Bacteria, J. Immunol. **28**:133, 1935; II. Hypersensitiveness and Immunity to Foreign Proteins: An Analysis of the Parts Played by the Tissues and Circulating Antibody in These Two States, ibid. **28**:161, 1935; Some Observations on the Question of the Various Manifestations of Antibody Activity Being Due to Separate Antibodies or an Immune Substance Acting Differently Under Various Conditions, ibid. **28**:241, 1935.

3. McMaster, P., and Hudack, S. S.: The Formation of Agglutinins Within Lymph Nodes, J. Exper. Med. **61**:783, 1935.

4. Spink, W. W., and Keefer, C. S.: Studies of Hemolytic Streptococcal Infection: II. The Serological Reactions of the Blood During Erysipelas, J. Clin. Investigation **15**:21, 1936.

as determined by this test. In 3 of the 4 patients who died antibodies were demonstrated, and in 2 of these it was possible to clear the circulating blood of organisms, but the presence of extensive focal lesions and multiple abscesses caused death. From these studies, as well as those recorded by Hare,[5] it is evident that in patients with bacteremia antibodies develop. This has always been found to be the case when the patients recover, and antibodies can also be demonstrated sometimes when death occurs. In the latter group antibodies may be present in sufficient quantity to clear the blood stream, but the patients die of extensive focal sepsis. In others no antibodies are demonstrable. It seems fair to say that the presence of antibodies in the circulating blood is of significance in the clearing mechanism. The final disposition of the organisms will depend in large part on the capacity of the body cells to inhibit their growth and to destroy them.

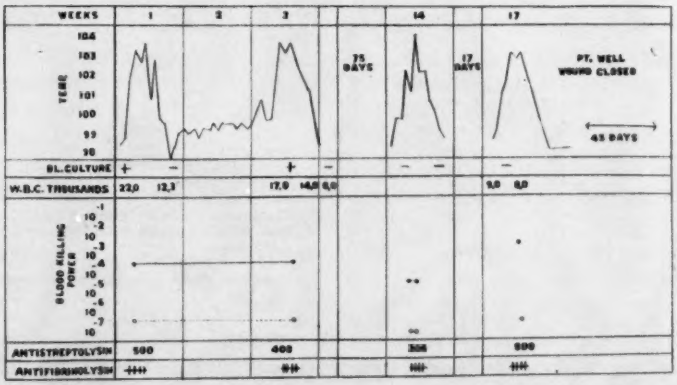

Chart 7.—Recurrent erysipelas of the thoracic wall following surgical incision of a sinus in the axilla. The attacks in the first and third weeks resulted from rupture of the local defense mechanism by surgical incision. The febrile reaction in the fourteenth week was due to an attack of acute tonsillitis, and the fourth febrile episode was due to an attack of erysipelas about the sinus tract. This chart indicates that rupture of the local defense mechanism may be followed by transitory bacteremia in spite of the presence of a high bactericidal power of the blood against the homologous organism. The solid dots indicate the patient's bactericidal power; the circles, that of the control.

From these observations it is not possible to state whether the antibodies are present before bacteremia takes place, but one can say that the presence of antibodies does not prevent the invasion of the blood

5. Hare, R.: Alterations in the Bactericidal Power of the Blood Which Occur During Hemolytic Streptococcal Infections in the Puerperium, J. Path. & Bact. **41**:61, 1935.

when the local defense mechanism is ruptured. This is illustrated in chart 7. A young woman with a chronic sinus in one axilla had recurrent erysipelas of the thoracic wall after surgical incision of the sinus. With the onset of erysipelas, bacteremia occurred. This was transitory, and at the time of this observation antibodies were demonstrated in the circulating blood. The second attack of erysipelas was accompanied with bacteremia and followed surgical incision of the sinus. The third and fourth febrile attacks shown in the chart were due to an intercurrent attack of acute tonsillitis and a final attack of erysipelas without bacteremia. It seems clear then that the blood stream may be invaded even when antibodies are present, but under these conditions the blood is often rapidly cleared of organisms.

BACTERICIDAL POWER OF BLOOD OF PATIENTS WITH LOCAL LESIONS

It has been postulated that local infections caused by hemolytic streptococci are due: (1) to infection with an organism of such low virulence

TABLE 5.—*Maximum Number of Hemolytic Streptococci Killed by 0.5 Cc. of Blood from Patients with Local Lesions Without Bacteremia*

Dilution of Organisms*	Total Number of Cases	Total Number of Controls
10^{-1}	18	4
10^{-2}	3	3
10^{-4}	1	5
10^{-6}	0	8
10^{-7}	0	2
Total	22	22

* 10^{-7} indicates from 2 to 7 organisms per 0.1 cc.

that it can be phagocytosed by normal blood [5] or (2) to the presence of an increase in the local and general resistance of the host for the particular infecting strain of bacteria, so that the spread of the infection is prevented. In other words, it has been suggested by one group of investigators that local infections are due to organisms of relatively low virulence, whereas those which invade the blood stream are of higher virulence. Another group maintains that it is a matter of the general resistance, as determined by the immune response of the patient. In regard to these questions there is no agreement, since the methods available for measuring the virulence of an organism are unsatisfactory and the results are difficult to interpret. It is now known that the blood of some normal persons is capable of phagocytosing and destroying hemolytic streptococci which have been isolated from the circulating blood, and it can be demonstrated that some normal persons are unable to phagocytose and destroy organisms that are derived from local lesions. These findings have been reported previously,[4] but for purposes of comparison they are summarized in table 5.

All the patients with local lesions could be shown to possess the capacity of destroying varying numbers of the homologous organisms, and this property of the whole blood increased during the course of the disease. The blood of normal controls did not contain antibodies for all strains of organisms, but antibodies for some strains were present. Here again it was not possible to say that the localized infection was due to the presence of antibodies prior to the onset of the disease, since none of the patients was studied before the initial attack. However, we have observed persons who have had recurrent attacks of erysipelas and who have had a good antibody titer in the blood preceding the attack.

As a whole, the evidence suggests that patients with local lesions without bacteremia have antibodies against the homologous organism, and these antibodies increase during the course of the disease. While it is possible for bacteremia to take place even when antibodies are present, these antibodies undoubtedly play a part in limiting the invasion of the blood and assist in the localization of the infection.

In summary it may be said that hemolytic streptococci that produce local or general infection in man belong to group A of Lancefield; they are strongly hemolytic and produce fibrinolysin and other toxic substances.

Patients with local hemolytic streptococcic infections have demonstrable antibodies in the blood, and the titer of these antibodies increases during the course of the disease. This property probably explains in part the reason for the localized infection. The presence of antibodies in the blood does not completely protect a person from a local infection or from bacteremia, since bacteremia may occur when there are antibodies present in the circulating blood if the local defense mechanism is ruptured by trauma or surgical interference. Furthermore, it can be demonstrated that patients with rapidly progressive infection may have no antibodies in the blood, whereas those that survive and in whom foci of infection develop invariably show antibodies. It has been stated by Hare [5] that at least half the patients who die of hemolytic streptococcic infections have antibodies in the circulating blood, and we have been able to confirm this observation. Three of our 4 patients who died (table 4) had demonstrable antibodies in the circulating blood. In 3 of the 4 the blood had been cleared of bacteria, but the patients died of multiple abscesses or of a local infection that could not be treated surgically. It does not seem unreasonable to suppose therefore that recovery from hemolytic streptococcic infection with bacteremia depends on the development of an effective local and general defense mechanism and that this depends in large part on a high grade of immunity and on the location of the infection.

MECHANISM OF BACTEREMIA

As has been stated, bacteremia may be considered to be the result of a loss of equilibrium between the normal clearing mechanism and the rapid overflow of bacteria from one or more foci of infection. It follows that the presence of bacteria in the blood will depend on the balance of these two factors. That is to say, when organisms are growing rapidly and overflowing into the blood faster than the clearing mechanism can eliminate them, bacteremia will follow. Or, when there is an overflow of organisms from a focus or foci of infection when the clearing mechanism has ceased to operate or is functioning at a low level of efficiency, bacteremia will result. Hemolytic streptococci are among the most invasive organisms producing disease. This invasiveness depends on the type of streptococci and the degree of general or local resistance of the tissues. In regard to the invasive qualities of the organism, certain facts have been gained by a number of investigators which aid in understanding this property. It is known that only a certain group of hemolytic streptococci are capable of producing disease in man and of invading the blood stream. This group includes the so-called group A or virulent human strains, according to the classification of Lancefield.[6] Tillett and Garner [7] have demonstrated that these organisms are capable of producing fibrinolysin, which is a substance that is capable of dissolving fibrin and perhaps of preventing the fixation of organisms locally at the site of invasion. Menkin [8] has marshalled evidence to show that hemolytic streptococci are unable to produce substances that injure tissues in such a way as to produce lymphatic thrombosis, and as a result the organisms can spread and grow freely in the lymphatic vessels draining a focus of infection. Ward and Lyons,[1] Hare [5] and others have shown that invasiveness depends in part on the ability of the organisms to resist phagocytosis. This property, in turn, depends on the type of variant, the capsular substance or the so-called opsonogenic substance of the organism. Undoubtedly other aggressive factors about which little is known at present may aid the organisms in invading the tissues. These are various toxic substances elaborated by the organisms, such as leukosidins and erythrogenic toxin. In any event, it is evident that this group of organisms is capable of producing chemical substances which enhance their free growth in tissues and invasion of the circulating blood.

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6. Lancefield, R. C.: A Serological Differentiation of Human and Other Groups of Hemolytic Streptococci, J. Exper. Med. **57**:571, 1933.

7. Tillett, W. S., and Garner, R. L.: The Fibrinolytic Activity of Hemolytic Streptococci, J. Exper. Med. **58**:485, 1933.

8. Menkin, V.: Inflammation and Bacterial Invasiveness, Am. J. M. Sc. **190**:583, 1935.

SUMMARY

From the clinical study of the 246 patients with bacteremia the following facts were elicited:

Bacteremia in hemolytic streptococcic infection is seen most often in patients in the first, fourth and seventh decades. These peaks of incidence correspond to the age incidence of infections of the throat and middle ear, the puerperal infections, and cellulitis and erysipelas.

The general fatality rate was 72 per cent. It was highest for the patients with cellulitis and erysipelas regardless of age, slightly lower for those with puerperal sepsis and lowest of all for patients less than 20 years of age with infections of the throat, middle ear and mastoid. Aside from the differences in mortality according to age and portal of entry, such factors as the duration of the sepsis, the location of infection in an area that could or could not be treated adequately and the presence or absence of debilitating diseases were of importance in determining the outcome.

The commonest metastatic lesions were in the joints, subcutaneous tissues and endocardium, although only about 30 per cent of the patients showed metastases.

Recovery following bacteremia occurred after a transitory invasion of the blood from a focal lesion without metastases or when the blood stream was cleared of organisms and focal infection was established if the lesion could be treated surgically.

Death occurred among those with debilitating diseases, those with rapidly spreading infection without localization and those in whom localization occurred in an area which could not be treated surgically (peritoneum, endocardium or meninges). Sometimes the blood was cleared of organisms, but the foci of infection were situated so that they could not be treated adequately.

From a study of the organisms which cause bacteremia and the immune reactions of patients with and without bacteremia the following statements are justified:

Organisms isolated from local lesions and from the circulating blood were beta hemolytic streptococci. They all belonged to group A of Lancefield, and they all produced fibrinolysin.

Organisms isolated from the circulating blood frequently resisted phagocytosis and were not killed by blood from normal persons. There are exceptions to this observation, but, by and large, it is true.

Organisms isolated from local lesions were phagocytosed by the leukocytes of some normal persons and killed in varying numbers by those of different persons. The blood of patients with local lesions usually possesses the capacity of killing the homologous organisms, and

this function increases with the course of the disease. The presence of circulating antibodies assists in localizing the infection and in preventing bacteremia.

In patients with bacteremia antibodies develop which aid in the clearing of the blood stream. In our experience all the patients with bacteremia who recovered had demonstrable antibodies in the circulating blood, and it was shown that antibodies were present in some of the patients who died, although the titer was low.

Bacteremia in hemolytic streptococcic infection is of greater value in prognosis than in diagnosis, and its presence may be taken as an indication of a loss of equilibrium between the local defense mechanism and the normal clearing mechanism. The presence of specific antibodies plays an important part in preventing bacteremia and in clearing the blood of organisms once it has become invaded by organisms from the local focus.

Progress in Internal Medicine

REVIEW OF NEUROPSYCHIATRY FOR 1937

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Many papers are written on psychiatry every year, but few deal with treatment. This year is an exception. Two new therapeutic methods have come into prominence; one has been discussed largely in the public press under the inexcusable name psychosurgery, and the other has caused a flood of literature in the medical press—the insulin shock treatment of schizophrenia.

"PSYCHOSURGERY"

Moniz, a Portuguese neurologist, well known for his studies on cerebral arteriography, and his colleague Lima [1] tried to alter by cerebral surgery the mental symptoms of twenty persons suffering from different psychoses; the condition presented by ten of these would probably be classified in America as severe agitated depression, three were manic and seven were schizophrenic. All those suffering from depression were improved by interruption of tracts in the frontal lobe; the results in the two other groups were dubious. In America Freeman [2] has taken up this work and reports on a small series of cases. His method is to introduce a "leucotome" through a small trephine hole and cut the white matter of the frontal lobe. (He calls it the prefrontal area, but how can an area be in front of the front?) With this instrument several balls of white matter are cut away from their connections and left in place. The operation is done blindly, and hemostasis is impossible. Thorium is injected into the hole afterward to show just where the white fibers were cut. As a rule from three to six lesions are made in each frontal lobe. In some cases of severe agitated depression there was a remarkable change. The patient became calm and less tense, and the mood improved conspicuously. In such cases this radical treatment occasionally seems justifiable: The patient is old, he is intensely unhappy and the prognosis is bad. Freeman, however, reports treating in this way patients with neuroses and young persons with schizophrenia. This mutilation of

1. Moniz, E., and Lima, A.: Premiers essais de psycho-chirurgie: Technique et résultats, Lisboa méd. **13**:152-161, 1936.

2. Freeman, W., and Watts, J. W.: Prefrontal Lobotomy in the Treatment of Mental Disorders, South M. J. **30**:23-31, 1937.

the brains of patients who might recover seems to me unjustifiable. Not only does "leucotomy" leave a necrotic mass of tissue and hemorrhage that may well cause cicatrix and epilepsy later, but thorium is a radioactive substance that may harmfully affect distant parts of the brain. Whatever the demerits of the procedure may be, it is an interesting physiologic observation that cutting off certain tracts beneath the frontal cortex will make a patient more placid. Somewhat analogous results have been obtained in monkeys by Jacobsen.[3]

THE TREATMENT OF SCHIZOPHRENIA BY INSULIN HYPOGLYCEMIA

Dementia praecox, or schizophrenia, as it is now generally called, is the most devastating of the major psychoses, both from the standpoint of bad prognosis and from that of economic waste, for it is a common disease, often starts early in life and may run a course of twenty or even forty years. The etiology is unknown, but there is good evidence that the disease runs in families [4] (i. e., that the seed is bad) and that environment plays a great rôle in developing the symptoms [5] (i. e., the soil is poor). These persons seem to be born tender; they are exquisitely vulnerable to the hurts of the world. Those with most marked involvement seem to deteriorate steadily, with little or no stimulus from the environment; those with mild involvement live relatively acceptable lives if they can be protected from the buffets of the world. The symptomatology can be roughly summed up as a withdrawal from reality into a world of fantasy. Until recently treatment has been largely symptomatic, and a few patients have been treated by psychologic means by those with much time and inexhaustible patience. But, on the whole, results have been disappointing and confused by the fact that from 25 to 30 per cent of the young patients have a long remission that may look like cure and a considerable number have one brief episode and regain a fairly normal equilibrium lasting for the remainder of life. In patients in whom the disease has run a course of several years, the chance of spontaneous remission falls to 5 or 10 per cent. For such a scourge, the victims of which occupy nearly two hundred thousand hospital beds in the United States, it is natural that any new treatment should be welcomed by members of the medical profession.

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3. Jacobsen, C. F., and Nissen, H. W.: Studies of Cerebral Function in Primates: Effects of Frontal Lobe Lesions on Delayed Alternation Habit in Monkeys, J. Comp. Psychol. **23**:101-112, 1937.

4. Cobb, S.: Review of Neurology and Psychiatry for 1935-1936, Arch. Int. Med. **58**:1111-1123 (Dec.) 1936.

5. Sullivan, H. S.: Environmental Factors in Etiology and Course Under Treatment of Schizophrenia, M. J. & Rec. **133**:19-22, 1931.

It has long been known that any situation which brings a schizophrenic patient near death may rid him temporarily of his mental symptoms. Burrows,[6] in 1828, recommended camphor in large doses to produce fits and cure "insanity," but he warned that in rash hands it may be dangerous to life:

> In a case of insanity, where two scruples were exhibited, it produced a fit, and a perfect cure followed. When given to the same gentleman two years afterwards, upon a relapse, i. e., a recurrence, it had the same effect, even to an alarming degree; but the patient did not, as before, progressively recover from a single dose, for it was repeated afterwards in smaller doses of ten grains.[7]

In like manner, major operations (if really major enough) for the "removal of foci of infection" or any other cause have been followed by remissions in mental symptoms, sometimes fairly long remissions and frequently short ones. Witness the colectomies performed about fifteen years ago on many inmates of hospitals for patients with mental disease. Moreover, it is an old story to psychiatrists that the occurrence of a severe infectious illness in a schizophrenic patient may cause the mental symptoms to disappear for a time. Inducing in these patients convulsions with metrazol [8] has had a similar effect, and periods of hyperpnea induced by breathing carbon dioxide and oxygen have brought about brief lucid intervals.[9] Most recently insulin hypoglycemia has taken the field. The only factor common to these different procedures is a severe metabolic change. It has been argued that the effective mechanism common to these different shocks may be psychologic—the schizophrenic patient is faced with a state of biologic urgency, often actually a fear of death. This state of terror is first induced and then relieved by a physician, and a new emotional situation is brought about. It can equally well be argued that some unknown chemical changes in the nerve cells are common to all these states, but it must be a basic change if caused by so many and such varied procedures.

The discovery by Manfred Sakel, of Vienna, that severe and repeated insulin hypoglycemia causes remission in many cases of schizophrenia has aroused great interest. His first publication appeared in

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6. Burrows, G.: Commentaries on the Causes, Forms, Symptoms, and Treatment, Moral and Medical, of Insanity, London, Thomas & George Underwood, 1828.

7. Dr. Diethelm, of New York, gave me this interesting reference.

8. Meduna, L.: Versuche über die biologische Beeinflussung des Ablaufes der Schizophrenie; Campher und Cardiazolkrämpfe, Ztschr. f. d. ges. Neurol. u. Psychiat. **152**:235-262, 1935.

9. d'Elseaux, F. C., and Solomon, H. C.: Use of Carbon Dioxide Mixtures in Stupors Occurring in Psychoses, Arch. Neurol. & Psychiat. **29**:213-230 (Feb.) 1933.

November 1934,[10] and reports from him and others corroborating the observations have followed fast. (The most important references[11] give a thorough review of the subject.)

Technic of Treatment.—In Sakel's own words, given in a recent paper,[12] the technic is as follows:

> The technique requires that the patient be given increasing doses of insulin until the so-called shock dose is reached; the size of the shock dose varies considerably in different individuals and may be anything from 15 to 450 units. The initial dose varies from 15 to 50 a day depending on the physical condition of the patient and the duration of his illness, and the doses are increased by 5 to 20 units daily until the shock dose is reached. . . . By shock dose we understand that amount of insulin which in any individual produces deep coma with areflexia within four or five hours after one injection. . . . A shock dose is given three to six times a week until the desired result is attained, but if the patient does not respond no more than 50 injections need be given . . . at least one to three days of rest are allowed every week. . . . The insulin injection is always given fasting and is followed in four or five hours by a sufficient amount of carbohydrates. . . . The neurological symptoms of hypoglycemia or coma are not dependent on any one blood sugar level. . . . Individual variations have to be made continuously, as therapeutic results cannot be achieved by a stereotyped repetition of hypoglycemic states measured by so many hours, but depends instead on the correct management of each individual hypoglycemic state, and especially on its termination at the right moment. These are matters which can be learned only through long experience.

The therapeutic aim is to find a dose and a time of termination of hypoglycemic symptoms which will produce the most desirable clinical

10. Sakel, M.: Schizophreniebehandlung mittels Insulin Hypoglykämie sowie hypoglykämischer Schocks, Wien. med. Wchnschr. **84**:1211 (Nov. 3); 1265 (Nov. 17); 1299 (Nov. 24); 1326 (Dec. 1); 1353 (Dec. 8); 1383 (Dec. 15); 1401 Dec. 22) 1934; **85**:35 (Jan. 5); 68 (Jan. 12); 94 (Jan. 19); 152 (Feb. 2); 179 (Feb. 9) 1935.

11. (*a*) Sakel.[10] (*b*) Dussik, K. T., nad Sakel, M.: Ergebnisse der Hypoglykämieshockbehandlung der Schizophrenie, Ztschr. f. d. ges. Neurol. u. Psychiat. **155**:351-415, 1936. (*c*) Wortis, J.: On the Response of Schizophrenic Subjects to Hypoglycemic Insulin Shock, J. Nerv. & Ment. Dis. **84**:497-506, 1936. (*d*) Langfeldt, G.: Die Insulin-Chokbehandlung der Schizophrenie, Psychiat.-neurol. Wchnschr. **38**:483-484, 1936. (*e*) Friedlaender, K.: Insulin-Chokbehandlung der Schizophrenie, ibid. **38**:520, 1936. (*f*) Glueck, B.: Hypoglycemic State in the Treatment of Schizophrenia, J. A. M. A. **107**:1029-1031 (Sept. 26) 1936. (*g*) Berze, J.: Die Insulin-Chok-Behandlung der Schizophrenie, Wien. med. Wchnschr. **83**:1365-1369, 1933. (*h*) Benedek, L.: Insulin-Schock-Wirkung auf die Wahrnehmung, Berlin, S. Karger, 1935. (*i*) Sakel, M.: Neue Behandlungsmethode der Schizophrenie, Leipzig, Verlag M. Perles, 1935. (*j*) Wortis, J.: Sakel's Hypoglycemic Insulin Treatment of Psychoses: History and Present Status, J. Nerv. & Ment. Dis. **85**:581-595, 1937. (*k*) Symposium on Therapy Including Hypoglycemia, Am. J. Psychiat. **94**:89-208, 1937.

12. Sakel, M.: The Methodical Use of Hypoglycemia in the Treatment of Psychoses, Am. J. Psychiat. **94**:111-129, 1937.

results. This may involve terminating at the end of an hour or so in the case of stupor, choosing as the time of termination the period when the patient is most responsive. Or it may involve termination just before coma or within a few minutes of the institution of coma in the excited patient or termination after a long period of coma in the paranoid patient.

The symptoms [13] of insulin shock may be divided into four groups: (*a*) The first group includes symptoms arising from the autonomic system—variation of pulse rate and blood pressure, drop in temperature, perspiration and salivation, pallor and flushing. Of these, the drop in temperature and the perspiration are the most constant and therefore the best indication of shock. (*b*) The motor symptoms start with restlessness and tremor, passing through various stages of twitching until pathologic reflexes appear. At the end there may be convulsions ending in muscular flaccidity and coma with areflexia. (*c*) The disturbances of consciousness start with sleepiness; then comes sleep from which the patient can be aroused; later he cannot be aroused and is in coma. (*d*) The mental syndrome is variable—the excited patient may become composed, or the stuporous patient may go into a state of extreme excitement.

The indications for terminating the treatment are deep coma with flaccidity, laryngospasm, generalized extensor rigidity of the muscles or severe convulsions, or tachycardia, Cheyne-Stokes respiration or a sudden fall in blood pressure late in coma. In about 7 per cent of the cases of shock early termination is necessary for one of these reasons.

Results of Treatment.—In *Science* for June 25, 1937,[14] the following statement is made: "More than 1,000 mental cases have been restored to health and sanity by treatment with insulin." It is difficult to amass the data necessary to make up a statistical review, because many of the reports have been recently made at meetings and are not yet available in print. Nevertheless, I feel that this statement was not justified. In the first place, the number of patients who have remission early in the disease is variously estimated to be from 20 to 30 per cent. Moreover, "restored to health and sanity" is phraseology not easily subjected to scientific analysis, and "full remission," "good remission" and "social recovery" apparently are not employed in the same way in the different clinics. A report on the Vienna series by Dussik and Sakel [11b] states that one hundred and four patients were treated. The authors consider that fifty-eight of these had a good remission, but they

13. Potzl, O.; Forstig, J. P., and Müller, M.: Seminar on Insulin at Vienna University Psychiatric and Neurologic Clinic, 1937, to be published.

14. Insulin in the Treatment of Schizophrenia, Science (supp.) **85**:10 (June 25) 1937.

divide their patients up into the new and the old ones. For the new ones (those who had had symptoms for only a year or less) there was a remission rate of 88 per cent, whereas for the old ones it was 48 per cent. Three died. Optimistic reports such as this are the ones quoted in the press, and they raise the hopes of many families. It is never emphasized sufficiently that a large percentage of the selected patients would have had a remission anyway and that remission is not cure.

The work in America is now actively under way, and preliminary reports were read at the meeting of the American Psychiatric Association in Pittsburgh last June. On the whole these are more conservative, but they are so recent that one cannot judge of their permanent value. Ross [15] reports on thirty-eight patients; nineteen had returned home since treatment, nine of those who remained in the hospital were improved somewhat and ten were not improved at all. Katzenelbogen [16] reports from the Phipps Clinic at Johns Hopkins Hospital on sixteen patients; six had a complete remission, and four showed moderate improvement. Wortis and his co-workers [17] report on thirty schizophrenic patients treated during the last eight months; there was full remission in eleven, "social recovery" in eight, improvement in two and no improvement in nine. Young and his co-workers [18] state that eighteen of their thirty-one patients had a good remission, thirteen showed "social recovery," seven were not improved and two died. As far as I can summarize the American figures that are available, they indicate that about half the patients treated (for the most part after careful selection) become well enough to return home for a time, as yet undetermined, and half obtain little or no benefit. About 1.5 or 2 per cent die. The results are obviously a good deal better than those obtained by the usual methods of hospitalization and general institutional care. In the hospitals where there are enough trained physicians to give careful individual attention to the patients' psychologic problems, the results in cases of early involvement are much better than those in the hospitals where the care is merely custodial. But there are not enough patients treated in this way to make statistics available.

15. Ross, J. R.: Report of the Hypoglycemic Treatment in New York State Hospitals, Am. J. Psychiat. **94**:131-135, 1937.

16. Katzenelbogen, S.; Harms, H., and Clark, D. A.: Experience with the Hypoglycemic Treatment of Schizophrenia, Am. J. Psychiat. **94**:135-152, 1937.

17. Wortis, J.; Bowman, K. M.; Orenstein, L. L., and Rosenbaum, I. J.: Further Experiences at Bellevue Hospital with the Hypoglycemic Insulin Treatment of Schizophrenia, Am. J. Psychiat. **94**:153-158, 1937.

18. Young, G. A.; Young, R. H., and Roucek, L.: Experiences with the Hypoglycemic Shock Treatment of Schizophrenia, Am. J. Psychiat. **94**:159-170, 1937.

Apparently the results from convulsions and shock after metrazol treatment compare favorably with those from insulin shock.[19]

It is not, however, the number of cases of remission which is most impressive; it is the experience of the physicians who have watched these patients through treatment that makes one realize that something very radical is happening to the psyche. Wortis and his co-workers [17] say:

> Our patients grew calmer and more collected after their first injections, grew more lucid and accessible thereafter, and then began to show insight—at first during hypoglycemia and later throughout the day as treatment progressed. Some cases relapsed during treatment but were revived again and in all our cases we have had to fit our treatment to the individual and vary our procedure accordingly.

Physiology and Pathology.—Whatever may be the ultimate outcome of insulin therapy, some important physiologic observations are being made on the patients. Hundreds of severe insulin shocks are being given to persons who are relatively normal except for their mental symptoms. Himwich and his colleagues [20] have found that the oxygen utilization of the brain is greatly decreased during hypoglycemic coma (average before coma, 7.09 volumes per cent; during coma, 2.46 volumes per cent). When the oxygen utilization is definitely decreased the Babinski sign appears; when this condition is prolonged all reflexes are lost.

Experiments on animals by Kerr and Ghantus [21] show that overdosage with insulin causes a marked decrease in the glycogen content of the brain of dogs and rabbits, but this decrease in the brain is less marked and is later than the decrease in the sugar content of the blood. The lowering of the sugar content of the brain appears to be due to an increased utilization of carbohydrate in the brain itself, since the concentration of free sugar in the brain is constantly less than that in the blood. A secondary lowering of the sugar content of the brain could occur owing to insufficient supply from the blood. The disturbances of the central nervous system after insulin treatment are due to both factors—increased utilization and insufficient replacement.

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19. Meduna, L.: Die Konvulsionstherapie der Schizophrenie, Psychiat.-neurol. Wchnschr. **37**:317-319, 1935. Meduna,[8] von Angyal, L., and Gyárfás, K.: Ueber die Cardiazol-Krampfbehandlung der Schizophrenie, Arch. f. Psychiat. **106**:1-12, 1936. Janz, H. W. Die diagnostische Verwertbarkeit einiger Methoden zur Provokation epileptischer Anfälle, ibid. **106**:267-295, 1937. Camp, W. J. R.: Pharmacology of Metrazol, J. Pharmacol. & Exper. Therap. **33**:81-92, 1928. Flaum, E.: Kritik der Kardiazolwirkung, Klin. Wchnschr. **14**:1543-1548, 1935.

20. Himwich, H. E.; Bowman, K. M.; Wortis, J., and Fazekas, J. F.: Brain Metabolism During the Hypoglycemic Treatment of Schizophrenia, Science **86**: 271-272 (Sept. 17) 137.

21. Kerr, S. E., and Ghantus, M.: Carbohydrate Metabolism of Brain: Effect of Varying Carbohydrate and Insulin Supply on Glycogen, Free Sugar, and Lactic Acid in Mammalian Brain, J. Biol. Chem. **116**:9-20, 1936.

The mechanism by which hypoglycemia may cause coma and convulsions is not known. There are some hints that it may be related to the action of neurohumors at nerve endings in the fact that dextrose inhibits the liberation of substances which sensitize tissues to the action of acetylcholine, a substance which inhibits certain convulsions.[22]

Another important line of investigation is the study of the "brain waves" during insulin hypoglycemia. Hoagland, Cameron and Rubin[23] have found that the encephalogram becomes broken up as hypoglycemia progresses; concurrently the alpha waves decrease in frequency per second and eventually disappear. As the patient comes out of coma the record becomes more even, and the alpha waves return. When muscular twitchings occur there are no waves such as appear in epileptic patients; the process is apparently electrically different. The variation in the number and in the size of large waves before and after insulin treatment may prove to be an important aid in controlling treatment.

Müller[24] has studied the symptoms of hypoglycemia exhibited by these patients and is most impressed by the fact that the actual amount of blood sugar seems to have little to do with the reactions. No symptoms appear unless the level of blood sugar drops to 60 mg. per hundred cubic centimeters, but the level may fall below 30 mg. before symptoms appear or they may be severe at levels only a little below 60 mg. These discrepancies may be due to differences in the method of collecting blood. Venous blood usually shows between 20 and 30 mg. per hundred cubic centimeters during coma. The systolic blood pressure rises, and the diastolic pressure may fall. There is usually tachycardia, up to 100 or 120 beats per minute, and the patient feels a rapid, pounding heart. Slow pulse and falling blood pressure are late and dangerous signs. The electrocardiogram may show a flattened T wave.

The gross and microscopic changes that may be present in the brain after severe hypoglycemia are well described by Moersch and Kernohan.[25] They performed autopsies on two persons who died of spontaneous hypoglycemia (hyperinsulinism). The lesions of this disease cannot be said to be identical with the cerebral changes following insulin shock, but physiologically and clinically the conditions have much in common. The brain of the first patient showed edema and widespread degeneration of the nerve cells in the cerebral cortex and diencephalon, with acute changes in the microglia and oligodendroglia. "There were

22. Gerard, R. W., in Luck, J. M.: Annual Review of Biochemistry, Stanford University, California, Stanford University Press, 1937, vol. 6, p. 435.

23. Hoagland, H.; Cameron, D. E., and Rubin, M. A.: The Electroencephalogram of Schizophrenics During Insulin Treatments, Am. J. Psychiat. **94**:183-208, 1937.

24. Müller, M., cited by Glueck.[11f]

25. Moersch, F. P., and Kernohan, J. W.: Hypoglycemia: Neurologic and Neuropathologic Studies, Arch. Neurol. & Psychiat., to be published.

practically no normal nerve cells in the cerebral cortex." In certain devastated areas no nerve cells remained, and there was degeneration of the underlying white matter. In the second case the histologic examination was less complete; but again there was a conspicuous loss of cells in the cerebral cortex and in the hindbrain, the tissue looked edematous and extravasation of red blood cells into perivascular spaces was noted. Another autopsy, described by Vonderahe,[26] revealed diffuse degeneration throughout the brain, with especially marked lesions in the hypothalamus.

Two cases have been reported in which cerebral hemorrhage followed the coma and convulsions of insulin treatment for schizophrenia. At the meeting of the American Neurological Association Keyes, Freed and Riggs reported a case in which insulin treatment for schizophrenia caused a prolonged convulsion, during which hemorrhage took place into the subarachnoid space, accompanied with hemiparesis and prolonged stupor. They observed petechial hemorrhages in the brains of five patients who died of hypoglycemia.

Salm [27] reports a case in which the patient under treatment with insulin went into coma as usual, had severe convulsions and could not be aroused. The temperature rose to 40 C.; the pupils were small and unequal. Death occurred on the eleventh day of coma. Autopsy showed hemorrhage about the third ventricle of the brain and small extravasations of blood in the substantia nigra and vegetative nuclei. In the cortex the nerve cells showed widespread degeneration such as is seen after asphyxia.

Taking this evidence from microscopic observation and comparing it with the physiologic evidence that there is a marked lack of oxygen during the coma, it seems reasonable to conclude that asphyxia of the brain may play an important part in the phenomena of hypoglycemic coma and convulsions. It also seems possible that severe insulin shock destroys a great number of cerebral nerve cells. Some of the changes described are doubtless reversible, but experimental work on animals indicates that most asphyxiated nerve cells go on to permanent degeneration.[28] Hemorrhages in the brains of animals after induced hypoglycemia from insulin are reported by two groups of workers.[29] These were

26. Vonderahe, A. R.: Personality Change in Hypoglycemia, J. Med. **17**:189-190, 1936.

27. Salm, H.: Benommenheitszustände in Anschluss an die Insulinshockbehandlung von Schizophrenen, München. med. Wchnschr. **84**:1047, 1937.

28. Gildea, E., and Cobb, S.: The Effects of Anemia on the Cerebral Cortex of the Cat, Arch. Neurol. & Psychiat. **23**:876-903 (May) 1930.

29. Baker, A. B., and Lufkin, N. H.: Cerebral Lesions in Hypoglycemia, Arch. Path. **23**:190-201 (Feb.) 1937. Steif, H., and Tokay, L.: Beiträge zur Histopathologie der experimentellen Insulinvergiftung, Ztschr. f. d. ges. Neurol. u. Psychiat. **139**:434-461, 1932.

usually in the basal ganglions but often in the cerebral cortex. A recent report by Schmid [30] that repeated hypoglycemic states cause no permanent lesions in the brain has been quoted by several protagonists of insulin treatment. This paper by Schmid, however, is a preliminary report on three guinea-pigs. One had fourteen and the other two only ten hypoglycemic periods each. The paper proves nothing. It must be granted, on the other hand, that most experimenters have given the animals more severe shocks than the schizophrenic human beings have received. Thus those authors [31] who wish to be conservative and give pause to the enthusiastic insulin therapists emphasize the human autopsy reports just quoted, while the enthusiasts pass over them, saying that cerebral damage occurs only in fatal cases, that in therapy the process remains within physiologic limits, i. e., the cell changes are reversible, and the cell returns to normal. My opinion is that there probably is destruction of cerebral nerve cells during coma and convulsions. Both the physiologic and the pathologic reports suggest strongly to me the probability that the cerebrum is partially asphyxiated for long periods during treatment. But losing these nerve cells may be relatively harmless; no one knows how many cells may be lost without causing mental impairment. Certainly there is a great reserve that is probably not called on for ordinary mental activity, and perhaps many of the patients are considered in "good remission" when they are simply living along and not disturbing their neighbors.

Theoretical Considerations.—Many of the writers on the insulin shock treatment of schizophrenia mention in passing the fact that here at last is a good chemical treatment for a mental disease, which proves that all this psychologic bosh was wrong. They do not use these words, but the implication is evident. It is to be deprecated that every first year student of medicine cannot be given a lecture on the logic of departmental relations in a medical school. He would then understand, once and for all (for I believe any one who can get into a good medical school has brains enough to see it), that anatomy, physiology and psychology are merely names for administrative departmental units; they are convenient pigeonholes to house the professors, but there is no scientific fact that makes a separation between the departments biologically reasonable. When Himwich [20] says "The ameliorations which occur . . . must be ascribed to functional changes in the brain," he is saying nothing that is not entirely self-evident. The brain is the organ of mind; its function is the integration of nerve impulses, the most complex integrations being called mental. Any change in menta-

30. Schmid, H.: Zur Histopathologie der Sakel'schen Hypoglykämieschockbehandlung der Schizophrenie, Schweiz. med. Wchnschr. **66**:960-961, 1936.

31. Cobb, S.: Shock Therapy, New England J. Med. **217**:195-196, 1937.

tion therefore involves "functional changes in the brain." Moreover, function is impossible without an organ that functions. The lines drawn between "organic and functional," "physical and mental," are illusory and result from a harmful sort of academic thinking. Regarding the problem of insulin shock, therefore, the psychologist may describe the behavior of the patient as he comes out of coma and may make use of his suggestible state of mind to change his thought content; the physiologist may determine the amount of sugar in the blood at various stages of the treatment; if the patient dies the anatomist will be interested in the petechial hemorrhages in the diencephalon or the degenerations in the cortical nerve cells. Each investigator has his problem, but in order to make progress each must know something of both of the other problems and must have respect for the workers and their data. At a meeting last spring when Dr. Sakel spoke, it was amazing to see the audience split up into two factions—the "organicists," whose attitude was "Here is proof at last that dementia praecox is an organic disease," and the "psychologists," who felt "Of course, nearly killing a man will change his mental content and bring him back to reality." No one seemed to realize that in biology it is never a question of *either* a functional *or* an organic problem but always a question of *both*.

In a paper read at the meeting of the American Psychiatric Association on May 14, 1937, Sakel [12] discusses his theory of the action of hypoglycemia on the brain. He is cautious and starts out by saying that the new treatment has no basis on biologic or physiologic principles such as scientific medicine usually demands. Nevertheless, since this treatment has been hit upon by chance, he thinks it should be made use of, not only for empirical therapy but, by working backward, for the elucidation of the cause of schizophrenia itself. This, he says, is difficult indeed, for "We know nothing either about the conditions or processes involved in normal thinking, to say nothing of the complicated processes that must be involved in an hallucination or delusion." (I applaud Sakel's caution, but I do not agree with his nihilism; I think there is a great deal of scientific data on all these subjects.) Having thus washed the slate clean, he proceeds to describe his "working hypothesis," which he admits is schematic, but necessary for the development of the method and technic. The nerve cell is compared to a "fuel engine" which has "excitant material" comparable to "fuel;" normal "tonus" is kept up in the nerve cell by "the proportional mixture of excitant and inhibiting hormones." The nerve cell is said to have two "valences" which are "saturated with the excitant hormone in order to preserve a normal tonus." If the valences are abnormally saturated, "abnormal relaxation of the cell" may result.

After reading two pages of this, my mind had a surrealistic picture of a gas-engine nerve cell with fuel, hormones, valences, tonus and

the power to relax. Since only contractile tissues and elastic bodies have the power to relax, the picture is not only confusing but preposterous. Such a naive mixture of physics, chemistry, physiology and circumlocution has rarely appeared in a medical journal. It is scientific hypothesis degenerating to mixed metaphor!

Sakel's explanation of why hallucinations and delusions disappear in hypoglycemic shock is equally fallacious. He postulates the thinking process on specialized and fixated "intracellular pathways," saying that "the youngest and most active pathways in the nervous system are the most sensitive to injury" and that "the special sensitivity of everything that is of more recent development, more complicated and more dominant," allows the hypoglycemia to stop the function of the pathways thus designated, sparing the others.

Nothing is known of "intracellular" pathways such as Sakel postulates. Dominant paths are often neither recent nor complex. It is not true that pathways of more recent development are as a rule more susceptible to injury than older ones. Noxious agents are known that strike selectively the older neurologic mechanisms and spare the newer—poliomyelitis affects the ventral horn cells of the cord, encephalitis lethargica the gray nuclei of the brain stem and methyl alcohol the optic nerves, all sparing the cortex—to mention only a few. As a clinical example, Sakel cites the case of a patient who ceased having hallucinations "just before the development of coma." Since coma is by definition a state of unconsciousness, it does not seem to me necessary to drag in this cumbersome explanation to account for the disappearance of a conscious phenomenon like hallucination as coma comes on. The author took "the risk of getting involved in mythology" (to use his own words) and succeeded in doing so. At present the clinical descriptions of progressive nervous disintegration during increasing hypoglycemia and of the reintegration after treatment are about as close as one can come to a theoretical conception of what is happening in the brain. Certainly something important is going on that improves the mental state of patients with dementia praecox. Nevertheless the treatment is not yet proved to be anything more than palliative, and there is some reason to believe that it may be causing permanent damage to the brains of patients who might spontaneously recover.

EPILEPSY

Electro-encephalography is proving to be useful in neurology, especially in the diagnosis of epilepsy.[32] At the meeting of the American

32. Gibbs, F. A.; Lennox, W. G., and Gibbs, E. L.: Electro-Encephalogram in Diagnosis and in Localization of Epileptic Seizures, Arch. Neurol. & Psychiat. **36**:1225-1235 (Dec.) 1936.

Psychiatric Association in May Lennox [33] described epilepsy as "cerebral dysrhythmia," meaning that sudden storms of irregular impulses spread across the brain of the epileptic person, giving rise to irregular waves on the electrical record. Jasper,[34] however, read a paper giving evidence that these waves are not so much a matter of dysrhythmia as of "hypersynchronism," his idea being that many small waves come together and by their unison make the large abnormal waves seen in epilepsy. Be that as it may, the instrument for recording cerebral waves is now a useful diagnostic tool, for even between clinical attacks of grand mal or petit mal there are many "larval attacks." These can be picked up on the electro-encephalogram, and they add greatly to one's security in making a diagnosis of epilepsy, for the histories are often not reliable and waiting to observe an attack is usually fruitless. Gibbs is using the records to control treatment.

Penfield,[35] after many years of work on the surgical treatment of epilepsy, has published the results in seventy-five cases. His technic is an improvement of that originally described by Foerster;[36] it consists of meticulous history-taking and neurologic examination, careful encephalography, with air in the arachnoid space and ventricles, and observation of a seizure if one can be induced by hyperventilation or hydration. With all these data in hand a decision is made as to the advisability of exploratory craniotomy. If the operation is performed, a bone flap is turned down, and the brain is inspected for lesions and explored with a stimulating electrode for a trigger point, that is, a point of low threshold from which a weak stimulus will precipitate a convulsive attack. Scars and adhesions that are found may be removed by clean dissection. Trigger points may be excised if not too near the motor cortex or speech centers. The technic is long and tedious and must be exquisitely carried out; otherwise more harm than good will be done. The results are encouraging; 32 per cent of the seventy-five patients with epilepsy were free from attacks after craniotomy, and 23 per cent were improved.

33. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Epilepsy: A Paroxysmal Cerebral Dysrhythmia, Arch. Neurol. & Psychiat. to be published.

34. Jasper, H. H.; Hawke, W. A., and Nichols, I. C.: Localized Brain Potentials in the Convulsive Disorders, to be published.

35. Penfield, W.: Epilepsy and Surgical Therapy, Arch. Neurol. & Psychiat. **36**:449-484 (Sept.) 1936.

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Book Reviews

Clinical Laboratory Diagnosis. By Samuel Levinson, M.S., M.D., and Robert P. MacFate, Ch.E., M.S. Price, $9.50. Pp. 877, with 144 engravings and 13 plates, 5 in color. Philadelphia: Lea & Febiger, 1937.

Among the recent publications dealing with clinical laboratory diagnosis, this book is noteworthy and unusual because each subject discussed is prefaced by a brief review of the anatomy, physiology and chemistry pertaining to the understanding of normal and abnormal findings. The subject matter is divided so as to deal with organs or systems by chapters, and each chapter contains only the simplest of essential technics, with the clinical significance of the findings pertinent thereto presented fully.

The first four chapters of the book deal with the examination of the secretions and excretions of the gastro-intestinal tract and include biochemical and pathologic, in addition to clinical microscopic, methods. Various technics are described for eliciting information regarding the status of the function of the various organs of each system, as well as demonstrating any lesion that may be present.

Chapter V discusses metabolism, with an introductory review of carbohydrate, nitrogen, fat and organic acid metabolism and a description of one method of estimating the basal metabolism. An account of the various dextrose tolerance tests and a few pertinent remarks on the acid-base equilibirum of the body also are given.

The chemical analysis of the blood is considered in chapter VI. This chapter is comprehensive and is an improvement over similar portions of other texts of this type. For each procedure the first paragraph outlines the principle of the method employed, thus tending to clarify the technic for readers not well informed in biochemistry.

Chapters VII and VIII, after a general consideration of the anatomy and function of the kidney, outline various methods of determining the normal and pathologic functioning of this organ, in addition to the chemical analysis of the urine. The authors have included tables of the various findings characteristic of the different forms of Bright's disease as well as of the inflammatory diseases of the kidney.

The section on hematology includes the routine and special procedures which are necessary for determinations of the quantitative and qualitative changes in all the formed elements of the blood. The latter part of chapter IX deals with a classification of the diseases of the blood and is clear, up-to-date and comprehensive.

Chapter X, the heading of which is "Immunology and Serology," deals chiefly with the Wassermann, Kahn and Kline tests for syphilis and the agglutination and precipitin tests for typhoid, tularemia and undulant fever. The examination of cerebrospinal fluid, with indications and contraindications for spinal puncture, the technic of spinal puncture and the interpretation of the findings, is dealt with in chapter XI.

As in all books of this type, one chapter is devoted to general bacteriology. Chapter XII of this text includes general bacteriologic technics, preparation of mediums, and stains and staining methods, which are of more interest to the laboratory worker than to the clinician.

The normal and pathologic findings for the sputum, with the routine procedures, including the typing of pneumococci by various methods and the findings characteristic of various pulmonary diseases, are given in chapter XIII. Cutaneous tests and other biologic examinations, including the hormone test for pregnancy, with the clinical significance of each, are considered in chapter XIV. Chapter XV is a résumé of the preceding portions of the text as applied to pediatrics and is a valuable asset to the book.

The remainder of the book, chapters XVI to XVIII, which is devoted to the analysis of milk and water, histologic technic, legal medicine and toxicology, is not directly pertinent to clinical pathology but is of marked assistance to persons engaged in clinical laboratory work. The appendix, which gives an outline for a course in clinical pathology, is of interest only to teachers of that subject.

The text, as a whole, because of its arrangement, is clear and brief, yet with no sacrifice of completeness, thus presenting a subject in terms easily understandable to the student and general practitioner as well as the specialist.

Diseases of the Respiratory Tract. Eighth Annual Graduate Fortnight of the New York Academy of Medicine. Price, $5.50. Pp. 406, with 56 illustrations. Philadelphia: W. B. Saunders Company, 1936.

In presenting this symposium on respiratory diseases the Graduate Fortnight has accomplished its purpose—to select a "subject of outstanding importance in the practice of medicine and surgery" and to present it from as many angles as possible. In the twenty presentations practically every important aspect of respiratory disease is touched on, including allergy; the common cold; diseases of the sinuses; laryngeal, tracheal and bronchial disorders; bronchoscopy; bronchiectasis; influenza; chronic pneumonitis; pneumonia in childhood; immunology; evolution and surgery in tuberculosis; pneumonoconiosis; emphysema; empyema; pulmonary tuberculosis and embolism; atelectasis and related conditions; carcinoma of the lung, and mediastinal diseases. The list of authors is impressive.

As with all works of multiple authorship, there are wide variations in the worth, thoroughness and clarity of each section. The sketchiness of the section on emphysema is an example. In the section on diseases of the larynx, trachea and bronchi an attempt to include all diseases of importance in a limited space reduces the context to the monotonous outline form of a compend and leaves no central thought with the reader. However, sections such as those on bronchiectasis and the evolution of pulmonary tuberculosis impart to the reader fewer concepts, but they are interestingly presented and leave a lasting impression.

The sections stressing pathogenesis and pathologic physiology, such as those on pulmonary tuberculosis by Miller, massive collapse by Henderson and immunity in tuberculosis by Rich, are ideal for the type of audience sought. A greater allotment of time and space to these presentations would add considerably to the value of the volume. There is at times some overlapping, which makes for smooth transition from one aspect of disease to another, but for the most part it is unnecessary.

The reader will become irked at times by the elementary nature of some sections but will be gratified in other sections by the authoritative summarization of the recent advances in respiratory diseases.

Les abcès du foie. By P. Huard and J. Meyer-May. Price, 65 francs. Pp. 390, with 98 illustrations. Paris: Masson & Cie, 1936.

Huard and Meyer-May present a discussion of hepatic abscess which includes a study of the medical literature and personal observations in 150 cases. They divide their material into eleven chapters on general statistics, surgical anatomy, etiology, pathogenesis and pathologic anatomy, symptoms and clinical forms, clinical differential diagnosis, hepatic puncture, roentgenography and roentgen surgery of hepatic abscess, geographic survey of the treatment of hepatic abscess, medical treatment and surgical treatment. At the end of the monograph the authors include 174 brief histories of cases, 43 autopsy reports and an extensive bibliography.

The subject in each chapter is discussed clearly and carefully. The correlation of etiology, anatomy and pathogenesis with the clinical manifestations of the disease is well done. The discussion of the technic and use of hepatic puncture for biopsy, exploration and injection of iodized poppy-seed oil is clearly presented from a practical standpoint. The authors doubt that all sterile abscesses of the liver should be considered amebic unless proved by microscopic demonstration of amebas. They cite the autopsy studies of Joyeux in nearly 100 cases of hepatic

abscess of Tonkin in which no amebas were encountered. Huard and Meyer-May, however, believe that pus-forming amebas deserve more etiologic consideration than is usually given. The authors have not attempted to simplify the clinical picture of hepatic abscess for diagnosis. They, like most French clinicians, probably have divided the disease into too many unnecessary clinical forms, thus complicating rather than simplifying the clinical diagnosis.

As a whole the monograph is clear and thorough. Although it presents nothing essentially new, it emphasizes the clinical significance of the disease and renders aid to the medical profession by presenting a comprehensive source of information on abscess of the liver.

The Management of the Pneumonias. By Jesse G. M. Bullowa, M.D., Clinical Professor of Medicine, New York University College of Medicine, and Director, Littauer Pneumonia Research Fund. Price, $8.50. Pp. 525, with 142 illustrations and 88 tables. New York: Oxford University Press, 1937.

In this book the whole story of pneumonia is told clearly and forcibly. The clinical picture of pneumonia first is dealt with, and then are described the laboratory and roentgen methods employed in diagnosis. The manner in which typing of sputum, blood cultures and agglutination tests should be carried out and the significance of these laboratory tests are particularly well presented.

The second section of the book deals with general principles of treatment. This also makes interesting reading for the clinician. It is thoroughly up-to-date, for even the therapeutic value of sulfanilamide and its derivatives is mentioned. The question of treatment is taken up sanely, and the author evaluates therapeutic results in terms of his own experience, which makes what he says all the more pertinent: "Diathermy has not been associated with a reduction in mortality among bacteremic patients." "We did not find that pneumothorax benefitted blood invaded patients, the group where therapeutic effort is really needed most." "We now use no whiskey or alcohol in the treatment of the pneumonias, regardless of habit."

All the details of treatment are described meticulously: how to put on a thoracic swathe properly, how to control dehydration and how to administer hypertonic solutions of sugar. Treatment with oxygen receives prolonged discussion, and the various means by which oxygen may be administered effectively are well illustrated. Serum therapy, of course, is fully discussed.

The prognosis of pneumonia is considered in a relatively short chapter. The final chapter deals with the complications of pneumonia and their management.

On the whole the book is readable from beginning to end and is one of the most valuable and comprehensive reviews of pneumonia that have been published in many years.

La vésicule biliare et ses voies d'excrétion. By M. Chiray, M.D., and I. Pavel, M.D. Second edition. Price, 120 francs. Pp. 863, with 203 illustrations. Paris: Masson & Cie, 1936.

The first edition of this book, published in 1926, was so well received that Chiray and Pavel were prompted to write the present edition, which is a complete revision of the first. Old chapters have been modified and new ones added. Many unnecessary discussions have been eliminated and more complete ones presented, especially the discussions on physiology and radiology. The section devoted to the radiologic aspects of diseases of the gallbladder and the biliary tract was written by A. Lomon.

The book is divided into five parts, which include the following: anatomy, histology and physiology; methods of examination; gallbladder syndromes; diseases of the gallbladder, and medical and surgical treatment. The discussions are thorough, covering the important work of European and American observers interested in the functions and diseases of the gallbladder and biliary ducts. The authors also present their personal observations and ideas on various aspects of the subject. At the end of each chapter there is a rather exhaustive bibliography, which

includes only articles published since 1926, when the first edition appeared. There are many enlightening figures and illustrations. Complete indices by author and by subject are included.

The reviewer recommends the book to the clinician. It is a thorough, up-to-date presentation of diseases of the gallbladder and the biliary tract. It is lucidly and exhaustively written and should serve, at least, as a good reference book.

Diseases of the Nails. By V. Pardo-Castello. Price, $3.50. Pp. 377. Springfield, Ill., Charles C. Thomas, Publisher, 1936.

This excellent monograph by a dermatologist particularly well qualified in the field is the only comprehensive survey of its kind in the English language. Dr. Pardo-Castello capably fulfills his purpose of making a complete yet simple summary of the subject. The first chapter deals with anatomy and histology and includes the newer concepts of the circulation of the nail bed and the chemical composition of the nails. The pathologic changes in the nails in general are outlined in the second chapter, which includes a table of the frequency of disorders of the nails. The following four chapters are concerned with disorders peculiar to the nails, onychodystrophies, ungual manifestations of dermatoses and of systemic diseases and congenital diseases of the nails, thus roughly classifying the types of changes in nails. Under each individual subdivision the most effective therapeutic measures are given clearly. Roentgen treatment, with its indications and dosage, is discussed briefly in the last chapter. An addendum includes a tabulation of occupations in which diseases of the nails are common and a list of ungual symptoms due to particular poisons. The book is supplemented by numerous good illustrations and a comprehensive bibliography.

This small book is unusually complete and has a definite place in any medical library as a reference work; it will be particularly valuable to most dermatologists, to whom the terminology and classification of this subject have always been somewhat confusing.

Recent Advances in Allergy. By George W. Bray. Third edition. Price, $5. Pp. 484. Philadelphia: P. Blakiston's Son & Co., 1936.

This is a comprehensive review of the present knowledge of allergy, in which the literature on the subject is reviewed and discussed and nearly three thousand references are listed. The manifestations of allergy are considered individually, and the etiology, pathology, diagnosis and treatment are ably presented. The common allergic reactions are treated at length, and those which are less common are described and discussed in less detail.

The general form of the third edition remains essentially the same as that of the previous editions, although the older material has been revised and condensed and certain parts have been rewritten. In the chapter on distribution of pollens, the hay fever-producing plants of the British Isles have been classified, and their relative importance in causing hay fever has been considered. Except for this chapter, which deals with the flora of the British Isles only, the subject of allergy in general is well covered.

This book is a practical and conservative presentation of the present knowledge of allergy, and the reviewer considers it worthy of a place in the library of any one interested in the diagnosis and treatment of this condition.

Zehn Vorlesunger über Kymographie. By Pleikart Stumpf. Price, 8.70 marks. Pp. 112, with 80 illustrations and 1 celluloid grid. Leipzig: Georg Thieme, 1937.

This little volume is an abstract of the large book by Stumpf, which was reviewed in these columns recently. For the ordinary physician who is not a specialist this brief compendium serves admirably to acquaint him with the essential facts of roentgenkymography. Those who are interested in more details are referred to the review of the larger work.

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